Translated from the Danish

by

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HYPOSPADIAS

WITH SPECIAL REFERENCE TO ÆTIOLOGY



MUNKSGAARD
1953

DENNE AFHANDLING
ER AF DET LÆGEVIDENSKABELIGE
FAKULTET VED KØBENHAVNS UNIVERSITET ANTAGET
TIL OFFENTLIG AT FORSVARES FOR DEN
MEDICINSKE DOKTORGRAD

København den 19 februar 1953

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PREFACE

The studies to be reported were commenced 1946 during my time of service in Surgical Clinic C of Rigshospitalet Copenhagen at the initiative of Professor *E Dahl Iversen* M D The essential part of the material however was collected while I was assistant to the University Institute of Human Genetics To its chief Professor *Tage Kemp* M D and to Professor *E Dahl Iversen* M D I owe a debt of gratitude for advice guidance and practical assistance rendered in the course of my studies

The patients were derived in part from Lying in Department B of Rigshospitalet in part from the following surgical departments University Clinics C and D of Rigshospitalet Departments I and V of the Copenhagen City Hospital Departments A and D of Bispebjerg Hospital the Aarhus University Clinic and the Aarhus County Hospital I am indebted to Professor *Ebbe Brandstrup* M D Professor *E Dahl Iversen* M D Professor *S Kjærgaard* M D Professor *Otto Mikkelsen* M D *Torben Knudtzon* M D Professor *Jens Foged* M D Professor *H Retlev Abrahamsen* M D Professor *V Alkjær* M D and *J Fabricius Møller* M D for having kindly permitted me to use the case records from their departments

Furthermore I want to thank those colleagues who have examined patients for me afforded me impulses through discussions or helped in other ways Quite particularly I am grateful to *Johs Dossing* M D for assistance in connection with the polysymptomatic similarity tests and to *H E Helweg Larsen* M D for guidance in statistical matters

Mr *Ole Tonnisen Frederiksen* afforded help in drawing the pedigrees and Miss *Gerda Olesen* in typing the manuscript

My thanks are due for economic support from *P Carl Petersen's Fond* and for a grant awarded me by *Vera og Carl Johan Michaelsen's Fond* after the investigations were concluded

Copenhagen, February 1953

Hans Rahbek Sorensen

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INTRODUCTION

Hypospadias is a congenital defect which in severe cases may be a cause of great concern to the patients and their parents. The worry is not only due to the difficulty of micturition and the fear that the patient will be unable to lead a normal sexual life, but also to the widespread idea that there is something inferior about malformed genitals. This inferiority complex is often fed by the attempts of well-meaning parents to hide their child's defect.

Surgical correction has been connected with great difficulties, and even though the results are constantly improving, a severe case may require several operations.

The deformity is generally considered inheritable by Mendelian dominance perhaps with failing manifestation. This opinion is based on the case reports of more or less thoroughly studied families. Therefore, the mode of inheritance has not yet been definitely established.

Object of the Present Study

This study was designed mainly to elucidate the heredity by a proband study including an investigation of the genetic relation between the various degrees of this deformity. This involved a determination of the incidence of the defect and of the fertility among the patients. In the course of the study, moreover, it proved necessary to look for aetiological factors other than genetic ones.

In addition, it was endeavoured to elucidate the relation of hypospadias to Goldschmidt's intersexuality theory by statistical genealogical methods.

This volume does not by any means pretend to be a monograph on

hypospadias. Many aspects are not considered. An analysis of the therapeutic results might have been desirable but the material was not suitable. In part it is derived from a period during which great advances have taken place within plastic surgery and in part the surgical methods used were so varied that an evaluation of the results would have been difficult. On the other hand the material may serve in evaluating the operative criteria.

Chapter I

MORPHOLOGY

Hypospadias is generally defined as the congenital opening of the urethra on the under side of the penis (*Kaufmann* (1886), *Frangenheim* (1928), *Schneider* (1928), *Johnson* (1929), *Jeanbrau* (1937), *McCrea* (1940), *Goldstein* (1946))

The abnormal orifice may be anywhere between the glans and the perineum so that the deformity may be more or less pronounced The appearance of the prepuce is characteristic It is split on the inferior aspect and situated dorsolaterally, forming a hood over the glans The latter is often somewhat plump flattened in the antero-posterior direction, and furnished with a groove on the under side or, more rarely, *with the fossa navicularis ending in a blind pocket on the tip* The frenulum is absent Proximal to the abnormal opening, the raphe divides into two more or less well-defined branches extending laterally and terminating on the dorsal aspect of the prepuce, at times in one or two rosette-shaped figures, "les yeux dorsaux" (*Ombrédanne* (1932)) Between the glans and the opening there is a mucosa-like strip of skin overlying a scar-like band causing a downward curvature of this part of the penis This curvature is sometimes increased by the tension of a short urethra and overlying skin which also pulls the corpora cavernosa back towards the perineum The curvature may be complicated by torsion of the body of the penis In severe cases, the penis is invariably smaller than normal but its smallness is due in part to the curvature as may be shown by successful surgical repair The scrotum is always cleft when the opening is situated proximal to the peno-scrotal junction, but in mild cases it may be normal or slightly bifid

In other words hypospadias is not only a localized urethral defect, but a malformation of the male external genitals, as *Ombrédanne* (1932) puts it "Les formes de l'hypospadias sont les differents degrés de l aplasie de la face inférieure de la verge".

or immediately proximal to the latter on the distal one fifth of the pendulous part

(2) *Penile hypospadias* with the opening situated more proximal at any point up to the penoscrotal junction

(3) *Penoscrotal hypospadias* with the opening in the immediate vicinity of the penoscrotal junction

(4) *Perineoscrotal hypospadias* with the opening between the two halves of the cleft scrotum or behind it

In classifying a case it is important to consider the situation of the opening in relation to the proximal part of the genitals without trying to straighten the curvature of the penis If that is attempted the opening is pulled forward the urethra is tightened and this gives a false impression of a milder case No such regard could be paid in a classification based on case records In the majority of cases however the classification did not cause major difficulties but it cannot be ruled out that exceptional cases may perhaps have belonged to one of the neighbouring groups

To designate the morphological transitions between normal genitals and hypospadias the following terms were used

Low seated opening The opening is situated on the glans It may be intranavicular but it is separated from the fossa navicularis by a transverse fold The prepuce is normal or slightly cleft



Fig 1
Juxtaglandular hypospadias bordering on penile hypospadias Stenosis of opening

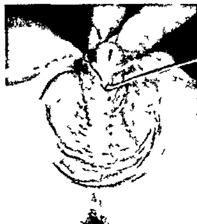


Fig 2
Penoscrotal hypospadias



Fig 3
Perineoscrotal hypospadias

Short urethra The penis is flexed downwards but the opening is of a normal situation The prepuce may be slightly cleft

Diagnosis

As a rule the characteristic appearance of the malformation makes the diagnosis an easy matter There have been cases however in which patients with hypospadias have spent a short or long period of their lives as girls because an erroneous sex diagnosis has been made at birth (*Neugebauer* (1908) *Kovacs* (1912)) an error which has been made in Denmark too (*Sand* (1940))

When hypospadias is associated with undescended testes there is a possibility of erroneous diagnosis As emphasized by *Sand* (1940) exploratory laparotomy is required to determine the sex with certainty This opinion is shared by *Hooks* (1949) At about the same time he received two patients with hypospadias and bilateral cryptorchidism Exploratory laparotomy showed the gonads to be ovaries in both cases This made him assume a more active attitude in examining his patients with hypospadias and in the course of a fairly short time he diagnosed one case of true hermaphroditism (with a left sided ovary and a right sided testis) Another case not yet completely examined was believed to have ovotestes

To-day an exploratory intervention involves *a very slight risk* *It is* therefore probably the best thing to ascertain the nature of the gonads

before undertaking plastic repair of the genitals in cases of hypospadias associated with uni- or bilateral cryptorchidism.

Injection of gonadotrophin at the age of puberty may perhaps show the trend of the development (*Diaz* (1943)) It must be mentioned in passing that injury may lend the genitals the exact appearance of hypospadias

Erroneous Diagnoses in the Present Material.

In Denmark the risk of a wrong diagnosis in hypospadias is probably slight to-day The midwives are well educated and physicians are very often in attendance If an error does happen, there are great chances of making it good at the prophylactic infant examinations, medical examinations of children below school age, and the examinations by the school medical officers

In one case of the present series a wrong sex diagnosis was made in 1928

Case with wrong sex diagnosis (the proband in Pedigree 77) At birth the sex was stated to be female In childhood, however the parents realized that "something was wrong with the genitals" The patient had no medical examination, was reared as a girl and attended a girls' school About the age of 14, however, the patient became strangely coarse, and when the sexual desire wakened it was directed towards girls The patient was very unhappy, believed for a time that he was homosexual, but gradually realized that he must be a man At a medical examination for another reason, the physician noticed the genital condition and took action An application for a male

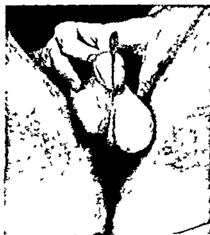


Fig. 4

Patient with penoscrotal hypospadias Probe in the urethra Penis partly erected The patient was reared as a girl

name was filed (through Professor Sand of the University Institute of Forensic Medicine) and granted The patient was then admitted to hospital for plastic surgery.

Admission examination The 19-year-old patient is somewhat below medium height, build and hairing masculine

External genitals (Fig 4) Penis greatly flexed downwards and gives the appearance of being rather small, but the corpora cavernosa are well developed The penis is situated between the two halves of a slightly cleft scrotum The prepuce is most developed on the dorsal aspect, absent on the under surface The glans is cleft on the under side The orifice is situated between the anterior part of the scrotal halves No rudimentary vagina Testes normal on palpation, with epididymides and vasa deferentia, and situated in the scrotum

Digital examination of the rectum An organ suggesting the prostate is palpable

Only one case of pseudovaginal hypospadias occurred in this series This type differs from the others by the persistent rudimentary vagina Morphologically it must therefore be considered a special variety which cannot be included in the proband material as a whole As the patient, however, is living as a woman, the case history will be briefly reported

Patient with pseudovaginal hypospadias living as a woman (The proband in Pedigree 174) The patient (Fig 5) had lived all the time as a woman but at puberty the breasts failed to develop, instead growth of beard set in The patient denied having any libido, had been engaged (as the female partner) for a time Recently nodules had developed in both groins

On admission, at the age of 29, the patient gave a masculine impression The voice was deep and the breasts undeveloped Hairing masculine with vigorous growth of beard and hairy chest Muscles well developed

External genitals Phallus 5 cm in length, as thick as the little finger Two genital folds dilated by bodies, as large as pigeon's eggs, which felt like testes with epididymides. The opening of the urethra was between these folds Behind the opening, there was a rudimentary vagina, about 2 cm deep ending in a blind pocket

Digital examination of the rectum revealed a band shaped structure extending from the floor of the rudimentary vagina towards the abdomen

Exploratory laparotomy showed a pelvis of masculine appearance, with deep rectovesical pouch, but no signs of a uterus or its appendages The gonads were seen on both sides They were somewhat atrophic testes, which otherwise looked normal, with epididymides and vasa deferentia Biopsies were obtained from both sides, and histological examination showed testicular tissue with atrophy, fibrosis, and an increased number of Leydig's cells The patient was made acquainted with the condition A change of name was proposed and the patient agreed, but after having been referred to Professor Sand, »she« changed her mind and went on living her life as a woman When seen later, the patient stated that the growth of beard bothered her most

The patient has a sister who was hospitalized and showed the same condition In this case however the testes had not descended

In addition there is a case of real diagnostic error, a case of true hermaphroditism diagnosed as hypospadias

True hermaphroditism diagnosed as hypospadias (the proband of Pedigree 175) Hospitalized for the first time at the age of six showing downward curvature of the penis with a dorsal prepuce The glans was cleft on the under side and from this side a band shaped structure extended to the urethral opening which was situated on the anterior aspect of the partly cleft scrotum The right testis was in the scrotum whereas the left one was in the superficial inguinal ring The downward flexion of the penis was corrected At the age of 13 the patient had left sided orchidomobilization and herniotomy The testis was found to be inverted outside the superficial inguinal ring There was a congenital hydrocele the abdominal part of which contained omentum Following isolation of the spermatic cord up to the deep inguinal ring the testis could be mobilized almost down into the scrotum

On several subsequent occasions the patient had plastic operations to reconstruct the urethra.

At the age of 15 the patient returned because of increasing swelling of the left half of the scrotum Puncture yielded a haemorrhagic fluid A tumor was



Fig 5

Patient with pseudo vaginal hypospadias living as a woman



Fig 6

A case of true hermaphroditism Testis on the right ovary on the left Funnel shaped urethral opening on the anterior aspect of the scrotum

palpable in the scrotum The patient was admitted and had exploratory laparotomy which showed the "tumour" to be a uterus In addition, a Fallopian tube and a normal ovary with follicular cysts The bleeding has presumably been an ovulation bleeding The right gonad was now exposed and proved to be a normal testis with epididymis and vas deferens Biopsy specimens of the gonads on both sides showed ovarian tissue on the left and testicular tissue with spermiogenesis on the right

A few weeks later the uterus tube and ovary were removed

Examination of the operative specimen revealed a small cavity in the uterus with endometrium in the early proliferative phase a normal tube and a normal ovary

This case raises the question whether the proband material may be considered uniform despite the even transition as regards the appearance of the external genitals In several cases the hypospadias may have been combined with undescended testes and the true nature of the gonads is not known

Writer's Morphological Studies

Incidence of Retained Testes in Hypospadias

The incidence of undescended testes in the various degrees of hypospadias has not been numerically elucidated An analysis of this nature is of particular interest to the present study since bilateral cryptorchidism is tantamount to sterility (*Torben Svend Hansen* (1945)) An increased incidence of cryptorchidism in hypospadias would therefore contribute to reducing the fertility and consequently influence the transmission of morbid genes if any

Moreover it would be interesting to ascertain whether an increased incidence of this phenomenon is peculiar to the severe forms of the condition as this might justify a sharper division of severe from mild cases

This analysis was based on the case records for patients with hypospadias admitted to the University Hospital Copenhagen Surgical Departments C and D the Copenhagen City Hospital Surgical Departments I and V the Bispebjerg Hospital Surgical Departments A and D and the Surgical Departments of the Aarhus University Clinic and the Aarhus County Hospital The material includes also cases of hypospadias occurring among the probands relatives The patients used later as probands were seen personally whereas in the remaining half mainly mild cases — the data are based exclusively on case records

The material is set out in Table I which shows that in a certain number of cases the records do not state whether the testes had descended

to the scrotum As these cases are counted as normal, the calculated incidence of cryptorchidism represents minimum values The material is classified not only according to the degree of hypospadias, but also according to age at the time of examination, since undescended testes often descend spontaneously during boyhood.

The results may be compared with other Danish studies of cryptorchidism at various ages Perusing the record cards of the School Medical Officers, *Engberg*, in *1948 found 1535 cases among 34,000 boys aged 6—7 years, i e an incidence of 4 51 % in this age group In Engberg's* opinion, however, the incidence is somewhat lower; he believes that some of the cases have been pseudocryptorchidism A follow-up exami-

Table 1.

Incidence of cryptorchidism in hypospadias *The material is classified* according to the degree of hypospadias and the patient's age

Degree of hypospadias	Testes in scrotum	Lacking data	Undescended testes				Total cases	Expected number with undescended testes
			right	left	both	total		
Juxtaglandular								
0—9 yrs	75	24	2	6	3	11	110	4 95
10—17 yrs.	17	4	—	—	—	—	21	0 32
18 and over	31	9	—	—	—	—	40	0 20
Total	123	37	2	6	3	11	171	5 47
Penile								
0—9 yrs	11	1	1	1	2	4	16	0 72
10—17 yrs	4	—	—	—	1	1	5	0 08
18 and over	6	—	—	—	—	—	6	0 03
Total	21	1	1	1	3	5	27	0 83
Penoscrotal								
0—9 yrs	12	1	1	4	7	12	25	1 13
10—17 yrs	4	—	1	—	3	4	8	0 12
18 and over	15	2	—	—	1	1	18	0 09
Total	31	3	2	4	11	17	51	1 34
Perineoscrotal								
0—9 yrs	8	—	—	3	2	5	13	0 59
10—17 yrs	3	—	—	2	1	3	6	0 09
18 and over	2	—	2	—	2	4	6	0 03
Total	13	—	2	5	5	12	25	0 71
Total cases								
0—9 yrs	106	26	4	14	14	32	164	7 38
10—17 yrs	28	4	1	2	5	8	40	0 60
18 and over	54	11	2	—	3	5	70	0 35
Total	188	41	7	16	22	45	274	8 33

nation of a large number of these boys after they had passed their 10th year revealed spontaneous descent in two thirds Perusals of the medical conscription protocols (cryptorchidism is a ground for rejection) *Engberg (1948)* and *Torben Svend Hansen (1945)* found 527 cases among 108 513 men ranging in age from 18 to 30 that is an incidence of 4 86 per thousand From a report on the work of the Baby and Child Health Stations (*Gort-* (19o1)) an estimate may be formed of the incidence of cryptorchidism in the youngest age groups In 1948 a total of 10 402 children were examined at the Child Health Stations of them 108 showed cryptorchidism which is an incidence of 2 08 % provided that half the children are boys At the Baby Health Stations where babies under one year of age are examined the corresponding incidence was only 1 12 % These values must be regarded with some reserve if only for the reason that the mothers can have the prophylactic examinations carried out also by their own physicians if they want them done at all This material is therefore selected and the criteria of selection are unknown

On the basis of the studies mentioned the following normal values will be used in the present paper

0— 9 years 4 5 % with undescended testes
10—17 1 5 %
18 years and over 0 5 % with

From these normal values which must be considered rather high the expected number of cases of hypospadias with undescended testes was calculated for the individual groups The results are given in the last column of Table 1

Table 2

Increasing incidence of undescended testes with increasing severity of hypospadias

	x / n	I in %	P in % / P in %
Juxtaglandular hypospadias	2 0	[illegible] 43	14 51 / 2 71
Penile hypospadias	[illegible] 0	18 52	47 34 / 5 43
Penoscrotal hypospadias	1–7	33 33	54 27 / 17 39
Perineoscrotal hypospadias	10 9	48 00	74 24 / 22 82
Total cases	5 4	16 42	24 40 / 10 58

Table 2 shows how many times the actual findings exceed the expected values $\left(\frac{a}{x}\right)$ in the different varieties of hypospadias. In addition the incidence $P\left(\frac{x}{n}\right)$ and its upper and lower confidence limit P_s and P_m were calculated according to the formula

$$\frac{1}{n+9}\left(x + 4.5 \pm 3\sqrt{\frac{x(n-x)}{n} + 2.25}\right)$$ Kemp (1942) l.c. p. 53.

The incidences found do not apply to all series of hypospadias as the patients' age influences the incidence of cryptorchidism. In the groups penile, perineoscrotal and penoscrotal hypospadias, however, the values show that the incidence of retained testes is increased in hypospadias, the lower confidence limit being higher than the 4.5 % in the youngest age groups of the normal series.

In juxtaglandular hypospadias the lower confidence limit is lower than 4.5 %. The actual number with undescended testes was therefore compared with the expected number by means of the χ^2 test. The result is $0.01 < p < 0.02$ ($f = 1$, $\chi^2 = 5.76$). The difference is not significant but extremely probable, particularly when considering that the normal values are rather high.

In 48.9 % the cryptorchidism was bilateral. In a series of 256 cases *Bjerre* (1935) found 36.7 % bilateral. In series of this small size the difference is not real. As *Bjerre* found only 16.3 % bilateral among 900 cases from the literature, the incidence of bilateral cases in hypospadias may still be increased.

It will be seen that an increased incidence of cryptorchidism is characteristic of all degrees of hypospadias, increasing with increasing severity of the hypospadias. This quantitative difference does not afford any justification for a morphological division of the mild and severe varieties.

The increased incidence of cryptorchidism and the possible relative increase in bilateral cryptorchidism entails a reduced fertility in hypospadias, particularly in the most severe degrees.

Chapter 2

INCIDENCE

Previous Investigations

Hypospadias is a fairly common defect Various authors have ana lysed the incidence but the results have varied owing to inadequate selection and a too small size of the materials in several instances

The highest incidence has been reported by *McCrea* (1940) Among 150 men he found hypospadias or a low seated urethral opening in 4 % The material is too small and nothing is stated as to how it has been collected

Mowry (1919) found 2 % among 10 000 soldiers suited only for limited military service It cannot be ruled out that hypospadias may have been the cause why a soldier has been declared unfit for full mili tary service This material is therefore possibly selected For the same reason the analyses of the incidence among patients with urinary tract diseases are of little value In series of this category *Barragan* (1911) has found 26 cases among 14 000 and *Burckhardt* (according to *Schnei der* (1928)) 22 among 1840

The best materials are *Rennes* (1831) 3000 recruits among whom 10 cases of hypospadias occurred and *Campbell s* (1947) post mortem series of 12 280 children with an incidence of hypospadias of one in 1100 boys

Hofmoll s finding (cited by *Langstein* (1910)) of only 13 cases in 104 446 children (the largest series reported hitherto) must be due to insufficiently thorough examination

Neugebauer s (1908) incidence of one in 1000 is presumably merely an estimate and it is not clear how *von Schurer* has arrived at his rate of one in 60 births

The incidence of hypospadias in Denmark has not been analysed From a report on the work of the prophylactic Child and Baby Health

Stations (*Gorlz* (1951)) it is apparent that during the first year of their existence — 1948 — 17 cases of hypospadias were found among 8242 babies under one year of age (Baby Health Stations) and 7 among 10,402 children aged 1—7 (Child Health Stations). Since, however, the prophylactic child examinations may be carried out by the child's own physician and are moreover voluntary, unknown factors may have caused a selection of the material. Nevertheless, a certain estimate may be formed of the incidence, which is rather more than 4 per thousand among the younger age group and less than 2 per thousand in the older group. This presupposes that half the children examined are boys. This difference in the incidence may be due to the small numbers involved, but it may also be due to incongruence between the two series.

Writer's Investigations

Determination of the Incidence among Newborn Babies

To this end, the writer chose the case records from Lying-in Department B, Rigshospitalet, Copenhagen from the year it was opened in 1910 up to and including 1945. In this department the newborn babies are examined for congenital defects at birth, on the rounds on the following day, and immediately before discharge. This series was, therefore, thoroughly examined. Nevertheless, all the mild cases had not been entered on the diagnostic card index, and therefore every record had to be perused.

A total of 60,680 records were perused. Among them there were 27 613 boys alive on discharge, 90 had hypospadias. The cases are described only in brief outline. Often the case records give merely the diagnosis. It cannot be ruled out that one case has been a low-seated orifice and another one a short urethra.

Including the last two cases, the incidence among the living discharged boys aged about 10 days (when mother and child are usually discharged) is one in 307 or 3.26 per thousand.

$$\left.\begin{array}{l} p_s \text{ per thousand} \\ p_m \text{ per thousand} \end{array}\right\} = \begin{array}{l} 4.46 \\ 2.38 \end{array}$$

(calculated according to the formula (*Kemp* (1942) p. 53)

$$\left.\begin{array}{l} p_s \\ p_m \end{array}\right\} \frac{1}{n+9}\left(z + 4.5 \pm 3\sqrt{\frac{z(n-z)}{n} + 2.25}\right)$$

General Validity of the Incidence Found

Most of these children were born of young, unmarried women who have a preference for admission to this department The material is, therefore, selected If *Büchi's* (1950) theory, viz that babies with hypospadias are more often born of young than of older women, holds good, the incidence found in the present material must be higher than among all newborn boys As shown later, the author is not in a position to confirm *Büchi's* theory, and no regard was paid to this selection of the series

There does not seem to be any reason to presume that patients with hypospadias are subject to a particularly high mortality *A priori*, however, it cannot be ruled out that an increased mortality may be caused, in part by the lesion itself and in part by a possible inferior general condition of the malformed babies If so, the incidence must decrease with advancing age, and that found in the present material becomes too high

Since the unmarried mothers are registered only by number (the names being entered in secret protocols) it was impossible to trace these 90 children in order to ascertain their viability Their birth weight did not differ significantly from that in normal series (*vide infra*) In this respect, therefore children with hypospadias do not show an inferior general condition To procure a material with which to compare the incidence of hypospadias among the newborn, all boys aged 7 14 in the municipal schools of Esbjerg on the west coast of Denmark were examined with a special view to hypospadias The defect was found in 13 out of about 2950 boys (*Jacobsen* (1949)) The material is not particularly large, but it accords well with that from the Lying-in Department, the incidence is 4 47 per thousand, p_s calculated per thousand being 0 87 and p_m 1 95

Hypospadias may pave the way for urinary tract infection, as the stenosis of the urethral opening, present particularly in mild cases, may give rise to dilatation of the urinary tract *Campbell* (1943) examined 152 children under 14 years of age with stenosis of the urethral opening Of them 98 % were congenital and some of these patients had hypospadias Urinary tract infection was present in 25 % *Fruhmann & Sternberg* (1930) have reported a case of hypospadias with stricture of the urethral orifice The patient succumbed to an ascending urinary tract infection

Several patients of the present series had stricture and urinary tract infection Only one patient succumbed to a urinary tract lesion

Juxtaglandular hypospadias with stricture of the urethral orifice and fatal kidney disease (the proband of Pedigree 118) The patient was admitted at

the age of 33 For the past 2 or 3 years he had been complaining of fatigue headache and swelling of the legs About one year before admission nephritis was diagnosed and treated with dietary measures The patient was admitted because of fatigue which except for brief periods had incapacitated him for the past year

On admission the patient looked quite well He had mild hypospadias with a small opening The urinary stream was thin Clinical examination revealed no other abnormalities No oedemas Temperature 37 5° C B P 170/125 Urine contained albumin Specific gravity about 1 010 increasing in the concentration test to 1 015 and decreasing on water tolerance test to 1 007

With some difficulty catheterization was performed with catheter No 8 It yielded a slightly bloody urine On microscopical examination the cell findings corresponded to the hæmorrhage No bacteria and no growth upon culture

Owing to the greatly impaired renal function bilateral decapsulation of the kidneys was performed a fortnight after admission (in March 1924) The kidneys were hard shrunk and granulated on the surface and there were fibrous adhesions to the capsule

Postoperative pyrexia and pulmonary symptoms The patient succumbed three days after the operation

Necropsy *Chronic nephritis sequels of nephrolysis bronchopneumonia* oedema of the lungs and pleurae chronic fibrinous pleurisy cystitis hypospadias Dilatation of the renal pelves or ureters was not observed

In this case the diagnosis was presumably glomerulonephritis The patient had not at any time exhibited signs of urinary tract infection He had no bacteriuria or dilatation of the urinary tract Therefore hypospadias associated with a slight stenosis of the urethral orifice can hardly have been responsible for the fatal issue

It is worth considering also whether an increased mortality may be caused by malignant degeneration in the retained testes which are unduly common in hypospadias (cf Chapter 1) *Carroll* (1949) has severely criticized the statistical investigations which have shown a relatively common malignant degeneration in retained testes He has moreover studied the problem by sending questionnaires to a large number of urologists He concludes *that* it has not been sufficiently proved that malignant tumours are particularly common in retained testes *that* malignant tumours of the testes are rare *that* they are extremely rare in cryptorchidism Accordingly there does not seem to be any reason to presume that this may lead to an increased mortality among patients with hypospadias Seminoma occurred in only one case of the present series

Perineoscrotal hypospadias with unilateral cryptorchidism Abdominal seminoma of unknown origin (The proband of Pedigree 141) A 24 year old man was admitted with the diagnoses *perineal hypospadias* inversion of the righ testis right sided inguinal hernia

The penis was rather small and downward flexed with dorsolateral foreskin which was cleft on the under surface The urethral orifice was *situated between the two halves of the cleft scrotum The left testis was* normal on palpation and situated in the scrotum whereas the right one was impalpable

The penis was straightened and orchidomobilization was performed on the right The right testis was small atrophic and inverted at the superficial inguinal ring

When 5 months later the patient was re admitted for plastic reconstruction of the urethra the right testis was at the superficial inguinal ring slipping in and out Moreover there was oedema of the right leg The patient complained of a feeling of tension in the abdomen No abnormality was detected by palpation or digital examination of the rectum Two months later a swelling was found in the lower abdomen Median inferior laparotomy revealed a large tumour which surrounded the iliac vessels on the right The tumour which moreover had invaded the coecum and the lower portion of the ileum was inoperable Histological examination of a biopsy specimen showed seminoma The tumour yielded to X radiation a total of 2800 r

At follow up three years after the operation there were no signs of recurrence The patient complained of attacks of subacute intestinal obstruction and the circumference of the right lower limb had increased by 5 cm

The point of origin of this tumour is unknown No tumour was at any time palpable in the normal left or in the atrophic right testis

Accordingly this material affords no evidence that an inferior general condition urinary tract infection or malignant testicular growths should give rise to essentially increased mortality among patients with hypospadias The incidence found among the newborn — *3 26 per* thousand — will therefore be used to represent the incidence among the entire male population

Incidence of the Various Degrees

Previous Investigations

The mild degrees are by far most common All *Rennes* (1831) cases were mild and so were most of *Mowry s* (1919) According to *Higgins* (1947) 70—75 % are of the glandular variety These values are presumably derived from a hospital series and accord well with *Barragan s* (1911) and *Burckhardt s* (cited by *Schneider* (1928)) findings of the glandular variety in 17 out of 26 and in 16 out of 22 patients respectively

Writer s Investigations

Table 1 (p 20) gives the incidence of the various degrees in a series consisting predominantly of hospital cases About 62 % were juxta glandular Perineoscrotal hypospadias made up only about 9 % This

does not however represent the incidence among the general population since it must be presumed that only the severe cases are hospitalized

In the series from Lying in Department B it is not possible to classify the hypospadias in all cases The case records which state only the diagnosis often add an adjective such as mild slight some or marked All the cases classified as penoscrotal or perineal however are thoroughly described

Since a follow up examination was out of the question the author tried to identify the cases with the patients from the surgical series by their — and in some cases the mother s — date and place of birth Two instances described as slight hypospadias and three as mild could be classified among the juxtaglandular cases One case called hypospadias was identified as a case of penile hypospadias None of the non classified cases could be identified as one of the two severe groups

Table 3

Classification of 90 cases of hypospadias among newborn boys

Short urethra	1
Low seated orifice	1
Juxtaglandular hypospadias	29
Mild hypospadias	8
Slight hypospadias	23
Some hypospadias	3
Hypospadias	8
Penile hypospadias	2
Marked hypospadias	4
Penoscrotal hypospadias	5
Perineoscrotal hypospadias	6

The exact incidence of the different degrees cannot be decided on the basis of the diagnoses listed in Table 3 At an estimate the juxtaglandular cases made up about three quarters the penile ones about one eighth and the penoscrotal and perineoscrotal together about one eighth

Chapter 3

FERTILITY

Previous Investigations

No report seems to have been published of the fertility in hypospadias. There is reason to presume, however, that in the severe degrees it is reduced. However, deformities severe enough to give occasion to a wrong diagnosis need not be tantamount to absolute sterility. *Neugebauer's* collected work from 1908 reports the case of a hypospadian living as a woman who impregnated her fellow servant, who gave birth to a boy with hypospadias.

In many authors' opinion (*Mayo* (1901), *Mowry* (1919), *Ombredanne* (1932), *Marx* (1938)) the fertility is reduced even in the glandular variety. *Mayo* (1901) goes as far as stating that the majority of the patients are impotent. In *Ombredanne's* (1932) opinion the fertility is reduced because the sperm is not slung towards the os externum uteri but instead deposited in the posterior fornix. No doubt these theoretical considerations have led to an incorrect result. At least part of the present series with glandular hypospadias published in 1948 (*Rahbek Sørensen*) did not show reduced fertility.

In the most severe cases the fertility is influenced by several factors. Complicating bilateral retention of the testes will prevent reproduction. Downward flexion of the penis makes coitus difficult. If the urethral opening is at the scrotum, it may be impossible to deposit the sperm in the vagina. The two last mentioned difficulties may be improved by surgery. This is no doubt what made the two German workers *Marx* (1938) and *von Schurer* (1939) propose that reconstruction of the urethra be performed only if the patient submits to sterilization so as to prevent the transmission of the morbid gene.

Writer's Investigations

Owing to the marked morphological differences between mild and severe cases between treated and untreated a numerical evaluation of the fertility in a given series is less interesting than an evaluation of the fertility in the various degrees and of the significance of treatment

The writer therefore investigated whether hypospadians marry as often as others Moreover the fertility of the married patients will be evaluated while due regard is paid to the extent of the defect and the result of treatment if any

Frequency of Marriage Among Hypospadians

The series includes 77 patients — probands and their relatives — aged 20 or over These cases are classified in Table 4 according to civil status age and degree of deformity This table also gives the expected number of married and single persons in the various groups of severity and age groups The expected values were calculated on the basis of the number of single men and the total number of men in the Danish population at the 1940 census (*Statistique du Danemark* 1945)

Despite the small figures involved the table shows a striking conformity between the actual and expected number of married and single patients in each of the four groups of hypospadians There are 30 single patients as against the expected 30 34

In other words hypospadians marry just as often as other men and the degree of the malformation does not appear to influence the frequency of marriage

Sexual Function

The married patients were questioned as to whether coitus caused difficulties and whether it could be accomplished to the satisfaction of both partners

Three patients had complaints in this respect

(1) The proband of Pedigree 129 A man aged 34 who married before his penoscrotal hypospadias had been treated Since sexual intercourse was carried out with difficulty and little satisfaction to either partner the patient was admitted for surgery after two years of married life A successful surgical correction and reconstruction of the urethra was performed At follow up about two years later the patient reported that now coitus could be performed without difficulty and to the satisfaction of both partners

(2) The proband of Pedigree 143 A 32 year old man with perineoscrotal hypospadias Surgical correction had been tried in several hospitals At

Table 4

Married hypospadians in various age groups compared with the expected rate of marriage

Age	Males in population		Juxtaglandular				Penile				Penoscrotal				Perineal			
			Actual		Expected		Actual		Expected		Actual		Expected		Actual		Expected	
	s	total	s	m	s	m	s	m	s	m	s	m	s	m	s	m	s	m
20—24	144553	160457	7	4	9.22	1.78	—	—	—	—	5	1	5.53	0.47	2	1	2.52	0.48
25—29	71073	161116	4	—	1.79	2.21	1	1	0.89	1.11	5	3	3.57	4.43	2	1	1.34	1.66
30—34	45376	157435	1	3	0.91	3.09		1	0.23	0.77	—	2	0.46	1.54		2	0.46	1.54
35—39	21415	141918	—	1	0.15	0.85		3	0.45	2.55	1	3	0.60	3.40		1	0.15	0.85
40—44	14520	128551	—	5	0.56	4.44		—	—	—	1	2	0.34	2.66		—	—	
45—49	10123	112144	1	1	0.18	1.82		1	0.09	0.91		1	0.09	0.91	—	—	—	—
50—54	8670	99156		6	0.52	5.48				—	—		—	—	—		—	—
55—59	7392	88158		1	0.08	0.92			—						—			
60—64	5830	75801		—	—	—				—	—				—	—	—	—
65—69	4245	57589		—	—	—	—		—	—		—	—	—	—		—	—
70—74	2935	40172	—	1	0.07	0.93			—		—		—			—	—	—
75—79	1761	21260	—	1	0.07	0.93	—					—	—	—	—	—	—	—
80	1291	18417		1	0.07	0.93			—	—			—	—	—	—	—	—
Total			13	24	13.62	23.38	1	6	1.66	5.34	12	12	10.59	13.41	4	5	4.47	4.53

s = single — m = married

follow up the penis was somewhat small and flexed downward by a scar like band The urethral opening was at the penoscrotal junction The patient complained of difficulty in performing the sexual act

(3) The proband of Pedigree 162 A 35 year old man with previously treated penoscrotal hypospadias At follow up the penis was rather small and with marked downward flexion due to scar like bands The new formed urethra opened at the corona A fistula at the penoscrotal junction The patient complained of difficulty in performing the sexual act due to the flexion His wife hardly ever obtained orgasm in the patient s opinion because of the small size of the penis

In all three instances the difficulty in *performing the sexual* act was due to a rather marked flexion of the penis Many of the remaining patients had had surgical *correction of severe flexion before marrying* but even so several had slight to moderate flexion of the glans or the penis (cf Tables 5—8) According to the patients statements such flexion has not caused any discomfort Perhaps these statements should be accepted with some reserve especially as regards the wife s satis faction It seems however that the matrimonial relations and sexual intercourse of hypospadians do not differ essentially from normal once severe *flexion has been corrected The fertility then depends only* on the more or less adequate deposition of the sperm and on the quality of the latter

Fertility and Morphology

In an endeavour to evaluate the fertility of each degree separately each group was tabulated separately The tables (5—8) give each pa tient s *age morphological features number of children and abortions* and by comparison the number of children begotten by his normal married brothers

Juxtaglandular hypospadias

The cases are presented in Table 5 which comprises 24 patients All but three had children Two of the last mentioned patients wives how ever *had had miscarriages* one of them twice because of intoxication of pregnancy This couple did not want another pregnancy One mar ried man aged 50 was *childless against his will*

The number of children ranged from 1 to 8 averaging 2 26 In com parison 23 normal brothers had an average of 1 70 children each

No difference in fertility could be demonstrated between the treated and untreated cases

Penile Hypospadias

Table 6 presents 6 patients all of whom had children ranging in number from 1 to 3 and averaging 1 67 Nine normal brothers had on the average 1 56 children each In this group no difference was found in the fertility of treated and untreated cases (or cases in which the treatment had been unsuccessful)

Penoscrotal Hypospadias

Of the 12 patients listed in Table 7 four had children Moreover the wife of a 24 year old patient had had two miscarriages The wives of seven patients had never been pregnant In one of these cases the sterility was due to bilateral retention of the testes

The four fertile patients had 4 4 2 and 1 children respectively The average number of children per patient was 0 9? Five normal brothers had an average of 1 8 children All the patients had been treated Among the fertile ones the reconstruction of the urethra had been a failure in two (with 4 and 2 children) and partially successful in two (with 4 and 1 children)

Perineoscrotal Hypospadias

This group comprises only five patients who are listed in Table 8 *None of the patients had children In three of these cases the sterility* is explained by bilateral cryptorchidism In addition one patient with left sided cryptorchidism had been hospitalized at an adult age because of right sided epididymitis In the remaining case the testes were normal but the urethral opening was situated between the two halves of a cleft scrotum

In juxtaglandular hypospadias the fertility appears to be normal and in the penile variety it is not definitely reduced In these two varieties treatment does not appear to influence the fertility

In penoscrotal cases the fertility must be presumed to be reduced in untreated cases or in those in which treatment has failed although the possibility of procreation is present *This series does not permit con*clusions regarding the influence of successful treatment on the fertility as it dates several years back and therefore includes few successful corrections

Table 5.
Juxtaglandular hypospadias
Fertily and morphological features

Pedigree No Status in family	Age	Treated	Flexion	Site of urethral opening	Fistula	Site of testes	Number of children	Number of mis-carriages	Number of brothers without hypo spadias	Number of brothers children	Number of children per brother
2 Father	53	no	Slight of glans	Corona	None	Scrotum	3	3	2	1	0 5
6 Paternal grandfather	80	no	None	Corona	None	Scrotum	7	0			
8 Paternal uncle	55	no	Slight of glans	Corona	None	Scrotum	4	0	4	12	3 0
9 Proband	71	no		Corona	None	Scrotum	8	0	2	1	0 5
25 Proband	22	yes	Slight of glans	Glans	None	Scrotum	0	1	0		
50 Proband	23	no	Slight of glans	Corona	None	Scrotum	1	0	0		
51 Proband	44	yes	Slight of glans	Glans	None	Scrotum	0	0	0		
12 Maternal grandfather	52	no	None	Corona	None	Scrotum	2	0	2	0	0 0
12 Maternal grandfather's brother	52	no	None	Corona	None	Scrotum	1	0	2	0	0 0

54 Father	40	no	Slight of glans	Corona	None	Scrotum	4	0	2	4	20
55 Maternal grandfather	6	no	None	Corona	None	Scrotum	4	0			
69 Brother	0	no	None	Corona	None	Scrotum	0	2	3	8	27
72 Father	48	no	None	Corona	None	Scrotum	2	0	2	4	20
98 Father	41	no	Slight of glans	Corona	None	Scrotum	5	0	0		
107 Proband	32	yes	None	Prox to corona	None	Scrotum	1	0	1	2	20
108 Proband	32	yes	None	Corona	None	Scrotum	2	0	0		
110 Proband	37	yes	Moderate of glans	Corona	None	Scrotum	2	0	2	4	20
111 Proband	54	yes	None	Glans	None	Scrotum	1	0	0		
112 Proband	42	yes	Slight of distal part	Glans	None	Scrotum	3	0	1	2	20
113 Proband	23	yes	None	Corona	None	Scrotum	1	0	0		
114 Proband	22	yes	Slight of glans	Glans	None	Scrotum	1	0	0		
115 Proband	51	no	Slight of glans	Corona	None	Scrotum	1	0			
118 Proband	33	no	None	Corona	None	Scrotum	4	0			
119 Proband	42	no	Slight of glans	Corona	None	Scrotum	2	0	1	1	10

Table 6.

Penile hypospadias

Fertility and morphological features

Pedigree No Status in family	Age	Treated	Flexion	Site of urethral opening	Fistula	Site of testes	Number of children	Number of mis carriages	Number of brothers without hypo spadias	Number of brothers children	Number of children per brother
6 paternal uncle	48	no	Slight of penis	Distal part *of body*	None	Scrotum	1	0	4	6	1 5
57 Proband	29	yes	Slight of penis	Glans	None	Scrotum	2	0	1	2	2 0
66 Proband	36	no	Slight of distal part	Distal part of body	None	Scrotum	1	0	3	5	1 7
126 Proband	34	yes	Slight of glans	On glans	None	Scrotum	2	0	1	1	1 0
127 Proband	36	yes	Slight of glans	Distal part of body	None	Scrotum	1	0	0		
159 Proband	38	yes		Not followed up			3	0			

Table 7
Penoscrotal hypospadias
Fertility and morphological features

Pedigree No. Status in family	Age	Treated	Flexion	Site of urethral opening	Fistula	Site of testes	Number of children	Number of miscarriages	Number of brothers without hypospadias	Number of brothers children	Number of children per brother
69 proband	47	yes	Moderate of penis	Penoscrotal junction	None	Scrotum	4	0	2	8	4 0
73 proband	28	yes	Moderate of penis	Corona	Pinhead at radix	Scrotum	1	0	0		
72 proband	25	yes	None	Glans	1 small at radix 1 small in pend part	Scrotum	0	0	0		
80 *proband*	43	yes	Moderate of penis	Penoscrotal junction	Vestige of urethre at glans	Operated bilateral cryptorch	0	0	1	0	0
89 proband	30	yes	Slight of penis	Glans	Small near the tip	Scrotum	4	1	1	1	1
93 proband	24	yes	Slight of penis	Middle of pend part	None	Scrotum	0	2	0		
128 proband	35	yes	Slight of penis	Radix	None	Scrotum	2	1			
129 proband	34	yes	None	Corona	One at radix	Scrotum	0	0	0		
132 *proband*	40	yes	Slight of penis	Glans	2 on middle of pend part	Scrotum	0	0	1	0	0
133 proband	27	yes	None	Near radix	None	Scrotum	0	0	0		
162 proband	35	yes	Marked of penis	Corona	One at radix	Scrotum	0	0			
164 proband	39	yes	Slight of penis	Radix	None	Scrotum	0	0			

Table 8

Perineoscrotal hypospadias

Fertility and morphological features

Pedigree No Status in family	Age	Treated	Flexion	Site of urethral opening	Fistula	Site of testes	Number of children	Number of miscarriages	Number of brothers without hypospadias	Number of brothers children	Number of children per brother
138 proband	24	yes	Slight of penis	Glans	Very small in perineum	Bilateral cryptorch	0	0	0		
139 proband	28	no	Marked of penis	In a cleft scrotum	None	Bilateral cryptorch	0	0	0		
142 proband	31		Not followed up			Bilateral cryptorch	0	0	0		
143 proband	32	yes	Marked of penis	In a cleft scrotum	None	Scrotum	0	0	1	1	10
172 proband	37		Not followed up			Left sided cryptorch Sequele of right sided epididymitis	0	0	0		

In perineoscrotal hypospadias the fertility is greatly reduced if only because of the high incidence of bilateral cryptorchidism It is difficult to say whether surgical treatment might render some of the patients fertile

From the point of view of genetics this means that the incidence of severe cases among the probands' fathers is lower than might be ex*pected according to the mode of inheritance*

Chapter 4.

PREVIOUS STUDIES ON THE HEREDITY OF HYPOSPADIAS

The heredity of hypospadias has never been elucidated by a proband study According to case reports, however, it is considered to be transmitted by irregular dominance (*Kemp* (1940), *Weitz* (1940), *Gates* (1946))

Kemp, in 1940, collected all familial cases published up to 1909, mainly on the basis of *Bulloch's* (1909) and *Neugebauer's* collected works This revealed that hypospadias had been reported

11 times in 2 brothers,
7 times in 3 brothers,
twice in 4 brothers,
once in 5 brothers,
9 times in father and son,
3 times in father, son, and grandson,
twice in 5 generations, and
once in 6 generations

Since that time no large families have been reported, but some surgeons (*Ombredanne* (1932), *Loughran* (1948), *Schaefer & Erbes* (1950)) have seen several familial cases

Reports of two or three cases in the same family are of little interest considering the common incidence of the defect. Large and thoroughly examined families, on the other hand, may give a hint as to the inheritance The largest family was reported by *Lingard* (1884) He found hypospadias through 6 generations in direct lineage In this family there was a striking number of cases, even when considering the dominant character of the defect It is not apparent however, how many of the patients *Lingard* had seen personally

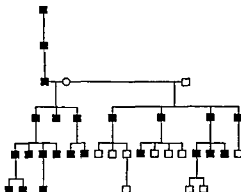


Fig 7
Lingard's family with hypospadias through 6 generations

In *Lesser's* family (1889) the inheritance appears to have been by irregular dominance Only two of the 11 members afflicted had been seen personally The data regarding the remaining 9 and the 4 persons who were presumed to be affected were given by the mother of the two subjects examined Although *Lesser* states that this woman was trust worthy I do not attach much importance to this family knowing from experience that information about hypospadias in relatives supplied by members of the families is extremely unreliable

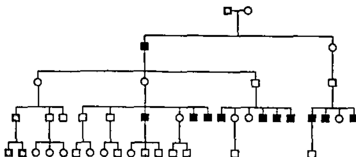


Fig 8
Lesser's family with irregular dominance

Also in *Strong's* family (1906) (cited by *Bulloch* (1909) with hypo spadias in 5 generations the affected members had not been examined personally The data were supplied by a patient with juxtaglandular hypospadias Therefore this family also is of little interest

In several instances, concordant hypospadias has been observed in monozygotic twins (*Lehmann* (1936), *Steiner* (1936), *von Verschuer* (1940), *Rhodes* (1943)) Moreover, *Camerer* (1938) has reported a case of discordance in monozygotic twins.

Lamy (1952) has collected a twin material of three pairs of concordant and three of discordant monozygotic as well as of four pairs of discordant dizygotic twins These twins were part of a twin material exceeding 900 pairs collected from schools and hospitals in Paris

The studies mentioned above have not definitely established the hereditary nature of hypospadias Since discordance has been found in monozygotic twins, exogenous factors must play a certain ætiological rôle Exogenous factors may be imagined to act upon both twin foetuses at the same time and thus make for concordance which in that case is independent of mono- or dizygocity *Lamy's* twin material indicates the ætiological rôle of heredity, as concordance was encountered in monozygotic, but not in dizygotic twins The numbers involved are, however, too small to make the difference statistically significant

Chapter 5

MODE OF COLLECTING AND EXAMINING THE PRESENT SERIES

In order to elucidate the heredity of hypospadias the writer collected a proband and a twin material The incidence found in these series was then compared with that found among the newborn and schoolboys (cf Chapter 2)

Selection of Probands

As probands the writer selected patients admitted to Surgical Departments C and D of the University Hospital, Copenhagen during the period 1915 to 1945, including a few out-patients This material was supplemented with cases of penile, penoscrotal, and perineoscrotal hypospadias admitted to Surgical Departments A and D of the Bispebjerg Hospital, Copenhagen, Surgical Departments I and V of the Copenhagen City Hospital, and the surgical departments of the Aarhus County Hospital and the Aarhus University Clinic

This proband material does not represent a cross section of the population, not merely because in the last six departments the mild cases were excluded, but also because a hospital material is bound to include more severe cases than mild The material was selected in this way, because the most severe cases are of most eugenic interest

Examination of the Proband Material

By personal application to each proband or his parents, if he was a child, the writer obtained the family history, examined the proband and asked for permission to apply personally to all male relatives All the male relatives were then visited and, if they did not refuse, submitted to an examination usually restricted to the external genitals

Relatives in military service were examined by the medical officers concerned and hospital patients by the hospital doctors A few relatives wished to be examined by their own physicians and a few living in distant parts of Denmark were also examined by their own physicians

True the examination of all male relatives was cumbersome and time consuming but it proved necessary as the proband s or his parents data very often did not conform to the result of the examination On the one hand there would be cases in the family about which they had no idea and on the other hand relatives believed to be afflicted proved to have normal genitalia

Effectiveness of the Examination

The majority of the patients (and parents) were willing to co operate but a few refused to give me permission to apply to the relatives In most of these instances the defect had been concealed from the greater part of the family I did not try to persuade these probands as it is difficult to realize the psychic suffering which might thereby have been inflicted on the often rather sensitive patients Instead I asked per mission to examine the closest relatives who knew about the defect In this way it proved possible to examine several relatives usually fathers and brothers Moreover this yielded further data and al about con sanguinity A few exceptional patients or parents however refused to have anything to do with this study Another few had to be excluded because they could not be traced were adopted or foster children or lived abroad

Accordingly the material is divisible into three groups

I 103 families examined
II 43 families partially examined
III 27 families excluded

To these 173 families may be added two which in fact do not belong to this material

IV A family with pseudovaginal hypospadias
A family with true hermaphroditism

Only 61 % of the families were examined as thoroughly as might be desired but there is no reason to believe that any selection of families with familial or with non familial occurrence of the defect has taken place Naturally enough a relatively large number of the patients with severe deformity did not want to have their relatives examined

Some of the relatives refused to be examined and were therefore ruled out From Table 9 it will be seen how many relatives refused to

have the examination and how large a percentage they made up of those who might have been examined This table furthermore contains a group called Others not examined comprising relatives living abroad sailors etc and a group of deceased relatives There is no reason to believe that this has made for a selection of malformed or non mal formed relatives

It is evident from the table that the percentage of refusal was higher among distant than among close relatives This accords with the ex perience that the more distant relatives are less interested in the study There is no reason to believe that the very persons who refused to be examined should be hypospadians

Table 9

Number examined and not examined in the various categories of relatives

	Examined	Refused to be examined	Others not examined	Deceased
Fathers	96	1 (1 03 %)		6
Brothers	83	1 (1 19 %)	1	12
Grandfathers	81	3 (3 57 %)	10	112
Paternal or maternal uncles	277	15 (5 14 %)	25	78
Cousins	563	34 (5 70 %)	59	54
Other relatives	410	21 (4 87 %)	31	31
Total	1510	75 (4 73 %)	126	293

Twin Material

The twin material comprises all boy twins contacted Six pairs of twins are contained in the proband material four pairs were derived from the case records of Lying in Department B one pair from the University Institute of Human Genetics and one from Surgical Depart ment C of the University Hospital

In most instances a polysymptomatic similarity test was used to decide the zygocity This test was in some cases supplemented by blood grouping In a few instances the diagnosis of monozygocity was based *on the appearance of the placenta In these cases there was one pla* centa two membranes in the septum and large superficial vascular anastomoses

Chapter 6

WRITER'S MATERIAL

THE PROBAND MATERIAL

The material was divided into the groups listed on p 44 according to the effectiveness of the examination

In addition the families examined were divided according to the severity of the proband's defect The familial cases are illustrated by pedigrees in which the following symbols are used for the males

- ☐ examined genitals normal
- refused to be examined
- not examined for some other reason
- died before the investigation was performed
- short urethra or low seated orifice
- juxtaglandular hypospadias
- penile hypospadias
- penoscrotal hypospadias
- perineoscrotal hypospadias
- ■ more severe malformation of the genitals

In other words each pedigree sets out the result as well as the effectiveness of the examination Families with solitary cases are listed in tables showing the number of relatives of each category who were

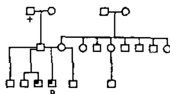
examined and the number of relatives who refused to be examined or who were not examined for some other reason as well as deceased relatives (Tables 10—13) These tables give also the number of sisters *and the total number of brothers in the family, the latter in brackets* after the number of brothers examined

The classification of the other groups of the material will be seen from the respective tables

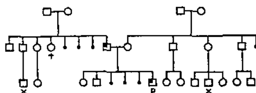
I Families examined

Probands with Juxtaglandular Hypospadias

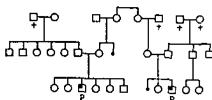
Pedigrees representing families with familial occurrence



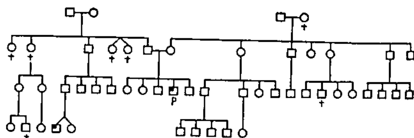
Pedigree 1



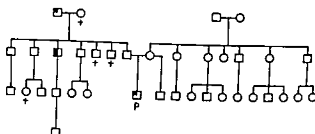
Pedigree 2



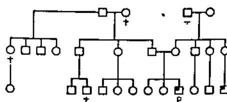
Pedigree 3 Pedigree 4



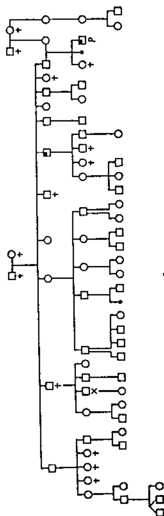
Pedigree 5



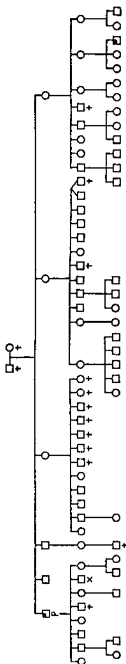
Pedigree 6



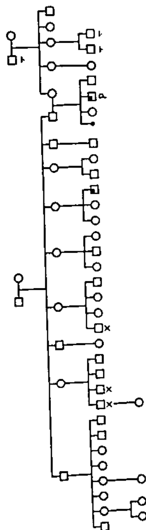
Pedigree 7



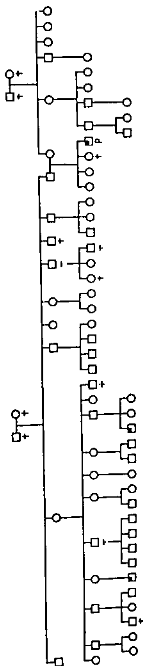
Pedigree 8



Pedigree 9



Pedigree 10



Pedigree 11

Pedigree 12

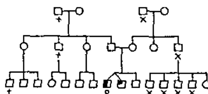
Pedigree 13

Table 10

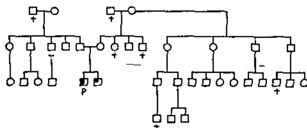
Solitary cases of juxtaglandular hypospadias

Pedigree No	Sisters	Brothers	Fathers	Sons	Grand fathers	Paternal and maternal uncles	Cousins	Others	Refused to be examined	Others not examined
14	1	2 (2)	1	0	2	4	6	0	0	0
15	0	0 (0)	1	0	1	3	3	0	0	2
16	0	1 (1)	1	0	1	1	2	0	0	3
17	1	1 (1)	1	0	1	1	7	0	2	1
18	1	0 (0)	1	0	1	0	4	0	0	1
19	1	0 (0)	1	0	2	1	2	0	0	0
20	2	1 (1)	1	0	1	4	7	1	0	2
21	1	0 (0)	1	0	1	1	6	0	3	2
22	0	0 (0)	1	0	0	1	1	0	0	5
23	0	1 (1)	1	0	1	0	0	0	0	2
24	0	1 (1)	1	0	2	1	3	0	0	0
25	1	0 (0)	0	0	1	1	0	0	0	2
26	2	0 (0)	1	0	1	4	5	1	0	4
27	1	0 (0)	1	0	1	1	0	0	0	1
28	1	0 (0)	1	0	1	3	6	0	1	2
29	0	0 (0)	1	0	0	0	1	0	0	2
30	0	0 (0)	0	0	2	6	17	4	1	1
31	2	3 (3)	1	0	1	4	10	0	0	6
32	0	2 (2)	1	0	1	3	4	3	0	4
33	1	1 (2)	1	0	2	2	4	0	4	1
34	1	0 (0)	1	0	0	3	2	1	0	3
35	1	2 (2)	1	0	1	1	2	0	0	1
36	1	0 (0)	1	0	0	2	4	0	0	5
37	0	1 (1)	1	0	0	1	5	11	0	4
38	1	0 (0)	1	0	1	2	2	0	0	1
39	2	1 (2)	1	0	1	4	2	6	0	5
40	0	0 (1)	1	0	1	6	10	0	0	10
41	1	0 (1)	1	0	1	12	17	18	0	9
42	2	3 (3)	0	0	0	2	3	5	2	6
43	1	2 (3)	1	0	1	1	4	2	1	5
44	1	1 (2)	1	0	2	3	7	1	0	4
45	0	0 (0)	1	0	1	1	9	13	0	5
46	0	2 (2)	1	0	0	2	6	0	0	2
47	1	1 (1)	1	0	1	1	2	10	0	[illegible]
48	4	0 (0)	1	0	1	2	10	0	0	[illegible]
49	0	1 (1)	1	0	0	2	2	3	2	6
50	1	1 (1)	1	0	0	4	11	15	3	5
51	1	0 (1)	1	0	0	1	6	14	6	6

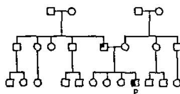
Probands with Penile Hypospadias
Pedigrees representing families with familial occurrence



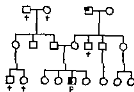
Pedigree 52



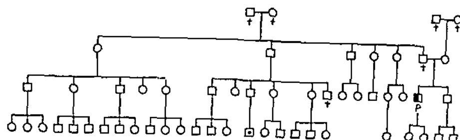
Pedigree 53



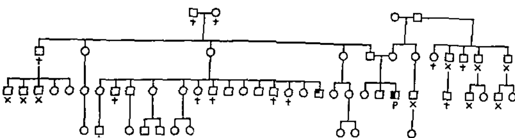
Pedigree 54



Pedigree 55



Pedigree 56



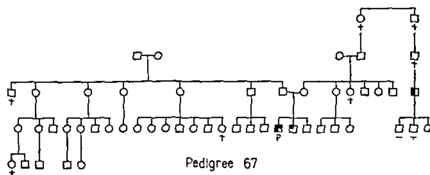
Pedigree 57

Table 11

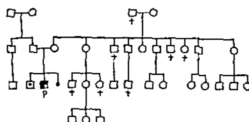
Solitary cases of penile hypospadias

Pedigree No	Sisters	Brothers	Fathers	Sons	Grand fathers	Paternal and maternal *uncles*	Cousins	Others	Refused to be examined	Others not examined
58	2	0 (0)	1	0	2	3	1	0	0	1
59	2	0 (0)	1	0	1	4	2	0	0	3
60	2	4 (4)	1	0	1	8	8	0	0	1
61	0	1 (1)	1	0	1	1	0	0	0	4
62	0	0 (0)	1	0	1	3	6	0	0	1
63	3	0 (0)	1	0	0	4	1	0	0	5
64	1	0 (0)	1	0	1	3	6	1	0	1
65	1	1 (4)	1	0	1	0	1	6	0	5
66	2	3 (4)	1	1	0	1	1	3	8	3

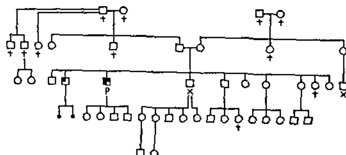
Probands with Penoscrotal Hypospadias
Pedigrees representing families with familial occurrence



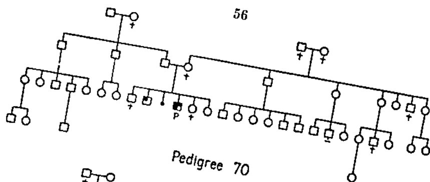
Pedigree 67



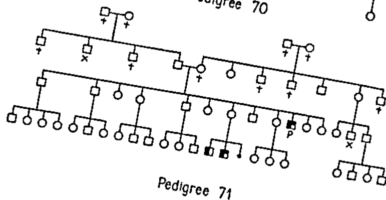
Pedigree 68



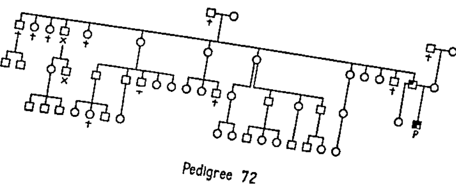
Pedigree 69



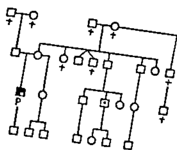
Pedigree 70



Pedigree 71



Pedigree 72



Pedigree 73

Table 12

Solitary cases of penoscrotal hypospadias

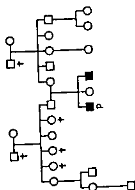
Pedigree No	Sisters	Brothers	Fathers	Sons	Grand fathers	Paternal and maternal uncles	Cousins	Others	Refused to be examined	Others not examined
74	1	0 (0)	1	0	0	3	1	1	0	2
75	1	1 (2)	1	0	1	7	4	0	0	2
76	5	1 (1)	1	0	1	2	1	0	0	10
77	0	3 (3)	1	0	1	2	3	0	0	2
78	0	0 (0)	1	0	0	1	4	1	0	2
79	0	0 (0)	1	0	2	7	4	0	0	0
80	2	1 (1)	1	0	0	0	1	5	3	7
81	0	1 (1)	1	0	1	1	1	6	0	1
82	0	0 (0)	1	0	1	1	5	1	0	1
83	2	3 (3)	0	0	1	2	2	2	7	7
84	2	0 (0)	1	0	1	6	23	10	3	8
85	1	0 (0)	1	0	2	0	1	0	0	0
86	3	0 (0)	1	0	0	3	19	6	0	5
87	1	3 (3)	1	0	0	3	14	26	1	7
88	0	1 (1)	1	0	0	6	24	4	0	5
89	0	1 (1)	1	1	0	6	12	16	0	10
90	2	1 (1)	1	0	1	1	3	4	1	1
91	5	0 (0)	1	0	0	5	12	7	0	8
92	1	0 (0)	1	0	1	6	5	2	4	3
93	1	1 (1)	1	0	0	3	12	19	1	8
94	1	0 (0)	0	0	0	1	8	1	0	3
95	2	0 (0)	1	0	1	4	28	26	5	22

Probands with Perineoscrotal Hypospadias

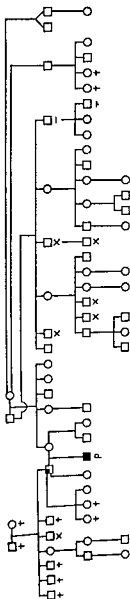
Pedigrees representing families with familial occurrence

P

Pedigree 96



Pedigree 97



Pedigree 98

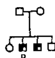
Table 13

Solitary cases of perineoscrotal hypospadias

Pedigree No	Sisters	Brothers	Fathers	Sons	Grand fathers	Paternal and maternal uncles	Cousins	Others	Refused to be examined	Others not examined
99	0	0 (0)	1	0	1	2	2	0	0	2
100	1	0 (0)	1	0	2	4	5	1	0	0
101	2	1 (1)	1	0	2	8	19	0	0	6
102	1	0 (0)	1	0	0	2	10	2	0	7
103	0	0 (0)	1	0	0	0	0	2	0	2

II Families Partially Examined

With familial occurrence



Pedigree 104



Pedigree 105

Families without known familial occurrence

Table 14

Number of relatives examined in partially examined families without known familial occurrence

Pedigrees Nos	Degree of hypospadias	Fathers	Brothers	Grand fathers	Others
106—122	Juxtaglandular hypospadias	6	8	8	24
123—127	Penile hypospadias	4	2	1	
128—136	Penoscrotal hypospadias	4	5	1	3
137—145	Perineoscrotal hypospadias	4	3		3

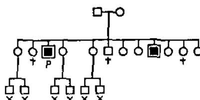
III. Families Ruled Out

Table 15

Reason why 27 families were not examined

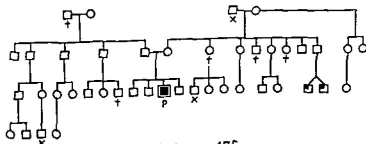
Pedigree No	Degree of hypospadias	Cannot be traced	Foster and adopted children	Refused to be examined
147—157	*Juxtaglandular hypospadias*	7	3	1
158—159	Penile hypospadias		1	1
160—166	Penoscrotal hypospadias	3	2	2
167—173	Perineoscrotal hypospadias	2	1	4
Total		12	7	8

IV Families of Interest, but not Belonging to the Material



Pedigree 174

Pseudovaginal hypospadias in two "sisters" (Case report on p 17)



Pedigree 175

True hermaphroditism (case report p 18) and juxtaglandular hypospadias in the same family

The Twin Material

Monozygotic Twins

Concordant

(1) Pedigree 52 Aged 10 years Alike physically so as to be mistaken at a distance also by their parents and mentally *Polysymptomatic similarity test* revealed *monozygocity* Both twins had *blood group* B *Genitals* I Penile hypospadias II Juxtaglandular hypospadias

(2) *Pedigree 12 Aged 54 years Looked so much alike that they were mistaken by their acquaintances Both had operations for right sided* inguinal hernia at a few years interval Began wearing spectacles because of farsightedness almost at the same time *Polysymptomatic similarity test* revealed monozygocity Both twins had blood groups A_1 N P C+c D E e+ Le (a) Fy (a+) Kell + *Genitals* Juxtaglandular hypospadias in both

(3) Pedigree 175 Aged 5 years Looked so much alike that they were mistaken by their acquaintances but not by their parents Both weighed 2000 g at birth *Polysymptomatic similarity test* revealed monozygocity Both twins had *blood groups* O M P+ C+ D+ *Genitals* Juxta*glandular hypospadias in both*

(4) University Hospital Lying in Dept B case rec 483/18 I weighed *1800 g and II 2200 g at birth* *Placenta* One egg with superficial vascular anastomoses *Genitals* Both infants had slight hypospadias of exactly the same appearance I died a few days after birth

(5) University Institute of Human Genetics Aged 39 years Outward resemblance so striking that they were mistaken by their acquaintances *Polysymptomatic similarity test* revealed monozygocity Both had *blood groups* O MN P+ C $\bar{c}$+D E e+ Le (+) Fy (a) Kell *Genitals* Examination of the penis showed in both twins the scar of a successful correction of hypospadias by the method of Beck By the appearance of the scar the defect must have been of the juxtaglandular variety in both cases

Discordant

(6) Pedigree 95 Aged 26 years Outward resemblance so striking that they were mistaken by acquaintances *Polysymptomatic similarity test* revealed *monozygocity* *Both had blood groups* O MN P+ C+$\bar{c}$+D+E Le (a) Le (b+) *Genitals* I Penoscrotal hypospadias II Normal genitals

(7) Lying in Dept B Rigshospitalet Copenhagen case rec 391/50 Birth weights I 3550 g II 2350 g *Placenta* One large placenta septum with two membranes superficial anastomoses between the two halves Both had *blood groups* A_2 P C+c̄+D+I ē+ Le (a) *Genitals* I Normal II Juxtaglandular hypospadias

(8) Lying in Dept B Rigshospitalet Copenhagen case rec 1514/51 Birth weights I 1900 g II 900 g No information regarding the placenta (the delivery took place at home) *Polysymptomatic similarity test* (at the age of 2½ months) revealed exactly the same eyes and ears Both had *blood groups* O N P+ C+D+I + I e (a+) I u (a) Fy (a+) *Genitals* I Normal II Penoscrotal hypospadias

(9) University Hospital Surgical Dept C case rec 702/52 Aged 15 years Birth weights I 3100 g II 3350 g *Placenta* Septum with two membranes Outward resemblance so striking that they were mistaken by their acquaintances *Polysymptomatic similarity test* revealed monozygocity Both had *blood groups* A_1 M P+ C+c̄+ D+I e+ I e (a+) Fy (a+) *Genitals* I Scar following operation for penoscrotal hypospadias by the method of Dennis Browne II Normal

Dizygotic Twins

Discordant

(10) Pedigree 31 Aged 12 years Are never mistaken for each other Polysymptomatic similarity test revealed dizygocity Both have *blood group* O *Genitals* I Normal II Juxtaglandular hypospadias

(11) Pedigree 32 Aged 6 years Are never mistaken for each other Birth weights I 2750 g II 2600 g *Polysymptomatic similarity test* revealed dizygocity *Genitals* I Normal II Juxtaglandular hypospadias

A pair of twins whose zygocity was not ascertained

(12) Lying in Dept B Rigshospitalet Copenhagen case rec 384/38 Birth weights I 1950 g II 1000 g *Placenta* Two completely separated placentae with a septum of four membranes *Genitals* II Hypospadias Died four days post partum

Chapter 7

EVALUATION OF WRITER'S MATERIAL

Uniformity

In this material the diagnosis of hypospadias had been made by clinical examination. As mentioned above, therefore some erroneous diagnoses cannot be ruled out among the cases combined with cryptorchidism, as the gonads were not always examined in exploratory laparotomy.

Although a natural grading is impossible, it would be interesting to investigate whether ætiological differences appear to exist between the different degrees set up artificially considering the marked morphological differences between mild and severe cases. From the genetic point of view, it must be ascertained, whether familial occurrence is met with in all degrees and whether intrafamilial variations occur.

Table 16 gives the incidence of familial cases classified according to the severity of the proband's defect. It is evident that familial cases were encountered in an average of 28.1 % of the families. When considering that the numbers involved are small, we find no difference in the incidence of the different degrees.

Studying the individual families with familial occurrence (including 104 and 105) with a view to intrafamilial variation, we find the same

Table 16

Incidence of familial cases grouped according to the severity of the proband's defect

Juxtaglandular cases	13	familial out of 51	(25.5 %)
Penile cases	6	„ „ „ 15	(40.0 %)
Penoscrotal cases	7	„ „ „ 29	(24.1 %)
Perineoscrotal cases	3	„ „ „ 8	(37.5 %)
Total cases	29	familial out of 103	(28.1 %)

(7) Lying in Dept B Rigshospitalet Copenhagen case rec 391/50 Birth weights I 3550 g II 2350 g *Placenta* One large placenta septum with two membranes superficial anastomoses between the two halves Both had *blood groups* A· P C+$\bar{c}$+D+1 $\bar{e}$+ Le (a) *Genitals* I Nor mal II Juxtaglandular hypospadias

(8) *Lying in Dept B Rigshospitalet Copenhagen* case rec *1514/51* Birth weights I 1900 g II 900 g No information regarding the pla centa (the delivery took place at home) *Polysymptomatic similarity test* (at the age of 2½ months) revealed exactly the same eyes and ears Both had *blood groups* O N P+ C+D+1 + Le (a+) Lu (a) Fy (a+) *Genitals* I Normal II Penoscrotal hypospadias

(9) University Hospital Surgical Dept C case rec 702/52 Aged 15 years Birth weights *I 3100 g II 3350 g Placenta* Septum with two membranes Outward resemblance so striking that they were mistaken *by their acquaintances Polysymptomatic similarity test revealed mono* zygocity Both had *blood groups* A_1 M P+ C+$\bar{c}$+ D+E $\bar{e}$+ Le (a+) Fy (a+) *Genitals* I Scar following operation for penoscrotal hypospadias by the method of Dennis Browne II Normal

Dizygotic Twins
Discordant

(10) Pedigree *31* Aged *12* years *Are never mistaken for each other Polysymptomatic similarity test* revealed dizygocity Both have *blood group* O *Genitals* I Normal II Juxtaglandular hypospadias

(11) Pedigree 32 Aged 6 years Are never mistaken for each other Birth weights I 2750 g II 2600 g *Polysymptomatic similarity test* revealed dizygocity *Genitals* I Normal II Juxtaglandular hypospa dias

A pair of twins whose zygocity was not ascertained

(12) Lying in Dept B Rigshospitalet Copenhagen *case rec 384/38* Birth weights I 1950 g II 1000 g *Placenta* Two completely separated placentae with a septum of four membranes *Genitals* II Hypospadias Died four days post partum

type in 14 families and a variation in the severity in 17 (cf Table 17) The variation may be so marked that the very mildest and the most severe cases occur in the same family

Since no difference is demonstrable in the incidence of the familial occurrence of the different degrees of the lesion *and since marked* intrafamilial variation in degree may be encountered the aggregate material will be considered as one in studying the etiological significance of heredity

Tabel 17

Degree of hypospadias in the malformed individuals within the same family

Same degree in 14 families

Juxtaglandular hypospadias 4 cases in 1 family
Juxtaglandular hypospadias 2 cases in 10 families
Penoscrotal hypospadias 2 cases in 2 families
Perineoscrotal hypospadias 2 cases in 1 family

Varying degree in 17 families

Low *seated* orifice and juxtaglandular hypospadias in 1 family
Low seated orifice and penile hypospadias in 1 family
Low *seated orifice and penoscrotal hypospadias in 2 families*
Juxtaglandular and penile hypospadias in 5 families
Juxtaglandular and penoscrotal hypospadias in 3 families
Juxtaglandular and perineoscrotal hypospadias in 2 families
Juxtaglandular — 2 cases — and penile hypospadias in 1 family
Juxtaglandular penile and penoscrotal hypospadias in 1 family
Penile hypospadias and 2 cases af penoscrotal hypospadias in 1 family

Incidence of the Defect Among the Probands Relatives

A total of 1590 relatives were examined *Twenty eight had hypospadias* and four well defined short urethra or low seated orifice In other words the incidence among the probands relatives is 1 76 % which is statistically higher — at the 1 % significance level — than that among *the total male* population which was 0 33 % Thus the standard error of the difference equals 0 52 % according to the formula

$$\sqrt{P(1-P) \times \left(\frac{1}{n_1} + \frac{1}{n_2}\right)}$$

(*Kemp* 1942 p 99) and 1 76 % — 0 33 % = 1 43 % > 2 58 × 0 52 % = 1 34 % The 75 relatives who refused to be examined give rise to an uncertainty but even though they are counted as normal the difference between the two groups is definite at the 1 % significance level since the standard error of the difference equals 0 51 % and 1 68 % — 0 33 % = 1 35 % > 2 58 × 0 51 % = 1 32 %

Table 18

Incidence of hypospadias among the various categories of relatives.

	With hypospadias	Without hypospadias	% with hypospadias
Brothers	10	94	9.6
Half-brothers	2	25	7.4
Fathers	4	111	3.5
Sons	0	17	0.0
Grandfathers	3	79	3.7
Paternal or maternal uncles	2	277	0.7
Nephews	2	58	3.3
Cousins	4	560	0.7
Others	5	337	1.5
Total	32	1558	2.0

The incidence in the various groups of relatives will be seen from Table 18. This table includes the 4 cases of low-seated orifice and short urethra, all of which occurred among the close relatives.

Concordance and Discordance among Twins

In Table 19 *Lamy's* (1952) twin material is compared with the present material of twins.

Table 19

Concordance and discordance among mono- and dizygotic twins.

	Monozygotic twins		Dizygotic twins	
	Concordance	Discordance	Concordance	Discordance
Lamy's series	3	3	0	4
Writer's series	5	4	0	2
	8	7	0	6

The χ^2 test, using Yates' correction (*Kemp* (1942), p. 128), shows a tendency that concordance is more common among monozygotic than among dizygotic twins ($\chi^2 = 3.15$, $f = 1$, $p = 0.07$).

Heredity

Since hypospadias occurs with an increased incidence among the relatives of hypospadians, and since concordance appears to be more

common among monozygotic than dizygotic twins, it must be inferred that the lesion is dependent on inherited factors

Although hypospadias occurs only in men, the gene may be transmitted by women (Pedigrees 3, 4, 7, 9, 10, 11, 12, 55, 57, 67, 71, 73, and 96) as well as by normal (Pedigrees 1, 5, 6, 8, 10, 11, 56, 57, and 73) and afflicted men (Pedigrees 2, 6, 12, 54, 55, 72, and 98)

As mentioned above, the lesion must depend on exogenous factors, as only 8 out of 15 pairs of monozygotic twins showed concordance. At 2 58 times the standard deviation — 99 % probability level — this means that concordance must exist in between 36 6 and 87 5 % of the monozygotic twins This corresponds to a degree of manifestation somewhere between 54 and 93 % (cf Kemp (1943) p 117—118) A similar degree of manifestation must be present in the proband material The mode of inheritance may, thus, be indicated by the degree of manifestation, since the numbers involved are too small to be treated by the usual statistical methods Table 20 lists the actual and expected number of cases occurring in some categories of relatives at dominant and recessive heredity respectively. The expected number was calculated on the basis of *Dahlberg & Hultkrantz'* formulas (*Kemp* (1943) p 112 —113) The actual number is 19 ± 2 58 × 4 36, while the expected number was 225 1 at pure Mendelian dominance At a probability level of 99 %, therefore, the degree of manifestation must be between 3 4 and 13 5 % providing dominant heredity with failing manifestation These values do not accord with the degree of manifestation calculated on the basis of the twin material, and this mode of inheritance is, therefore, unlikely In recessive heredity the expected number of cases is 50 3, corresponding to a degree of manifestation between 15 4 and 60 1 % with a probability of 99 % In recessive heredity with failing manifestation, thus, the degree of manifestation accords rather well with that in the twin material and the proband series Table 20 shows, moreover, a rather constant ratio between the actual number and that expected in the various categories of relatives, provided that the heredity is recessive This calculation, however, has the drawback of not holding good, if too many of the cases depend exclusively on exogenous factors In practice however, it may be expected that in a large series the cases are distributed as a lesion transmitted by recessive heredity with failing manifestation

Although the high incidence of hypospadias means that the gene of this lesion must be commonly present among the population, it must probably be assumed that the frequency of consanguinity is increased if hypospadias is a recessive character In 124 families, three cases of consanguinity occurred among the probands' parents This exceeds the

Table 20

Number of hypospadians in various categories of relatives compared with the number expected at dominant and at recessive heredity

	Total number of relatives	Dominant		Actual number	Recessive	
		Expected % affected	Expected number affected		Expected % affected	Expected number affected
Children	17	50.13	8.5	0	5.72	1.0
Brothers	104	50.11	52.1	10	27.80	28.9
Grandfathers Grandchildren Paternal and maternal uncles	367	25.21	92.5	5	3.01	11.0
Cousins Greatgrandfathers	565	12.75	72.0	4	1.67	9.4
Total	1053		225.1	19		50.3

ordinary incidence of consanguinity in Denmark, which is believed to be lower than 1 %. Owing to the small numbers involved, however, this finding cannot be attributed with much significance.

It may be concluded that hypospadias is dependent on exogenous as well as endogenous factors. The latter are probably transmitted as recessive characters.

Chapter 8

RELATION OF HYPOSPADIAS TO SOME INTERSEXUALITY THEORIES

An intersex is defined by *Goldschmidt* (1915) as an individual developing against its genetic sex According to the original sex, a distinction is made between male and female intersexes A distinction is made also (1931) between zygotic intersexuality in which the sex inversion takes place at the moment of fertilization, and hormonal intersexuality induced by the hormones of the opposite sex

Goldschmidt's Intersexuality Theory
(Zygotic Intersexuality)

Goldschmidt's intersexuality theory is briefly as follows

In male as well as female individuals the chromosomes contain both masculine and feminine sex determining factors These factors are inherited and may be of varying strength Weak and strong factors may be combined in a way so as to give rise to a divergence from normal in the ratio masculine and *feminine factors, and an intersexual individual results For instance, the* combination of strong masculinizing and feminizing factors in a genetically female individual results in a female intersex The mechanism of the development of intersex is explained as follows During early foetal life, the individual develops according to its original sex, but at some juncture, the turning point, the factors of the opposite sex prevail and after that time, the development takes the opposite direction If the preponderance of the opposite sex *is very strong the turning point occurs at an early stage of foetal life* and the individual develops markedly against its genetic sex

Goldschmidt (1911, 1915, 1931, 1933) proved his theory on the moth Lymantria in innumerable crossing experiments between various geographic varieties, the sex-determining factors of which were of varying strength By applying this theory to normal embryology and the mor-

phology of genital malformations *Goldschmidt* (1931) explained a large number of malformations in animals and man

As far as the human race is concerned the female is supposed to possess two feminizing and two masculinizing factors and the male one feminizing and two masculinizing factors In man only female intersexuality is said to occur Severe cases of hypospadias are regarded as female intersexes while the milder ones are interpreted as anomalies of developmental arrest as patients with mild hypospadias have had normal sons According to this theory female intersexes — who thus possess two X chromosomes — can have only daughters or intersexual children *Berblinger* (1936) shares *Goldschmidt s* view while *Mosczkowicz* (1936) has gone even further interpreting also mild cases of hypospadias retention of the testes and homosexuality as intersexual phenomena On the basis of embryological studies on the development of the masculine and the femine prepuce *Popper* (1937) states that the prepuce of hypospadians is feminine and he therefore subscribes to Mosczkowicz ideas

Writer s Investigations

In order to assess the validity of the intersexuality theory in hypospadias the writer employed the methods used by *Goldschmidt* in studying the Lymantria

(1) Sex distribution among the offspring
(2) Sex distribution in the sibships
(3) Occurrence of sex linked recessive characters in intersexes and their parents

Sex Distribution Among the Offspring of Hypospadians

The series counts a total of 68 persons with hypospadiac fathers Table 21 gives the sex distribution of these persons classified according

Table 21

The sex distribution among the children of hypospadians shows no divergence from normal

	Girls	Boys			
		Total	With hyposp	Normal	Not examined
Juxtaglandular hypospadias	20	27	3	17	7
Penile hypospadias	5	5		3	2
Penoscrotal hypospadias	5	6		4	2
Total	30	38	3	24	11

Table 22

Distribution of male and female individuals in the sibships, when *juxtaglandular cases* are interpreted partly as male, partly as female Good conformity with the expected number will be seen in the former, lacking conformity in the latter case.

Sibship		Hypospadians				Number of sibships $\times \sigma^2$
		Interpreted as males		Interpreted as females		
Size of	Number of	Expected number of males	Actual number of males	Expected number of females	Actual number of females	
2	23	30 667	31	30 667	39	5 106
3	15	25 710	31	25 710	30	7 350
4	9	19 197	23	19 197	22	7 038
5	6	15 486	16	15 486	20	6 492
6	4	12 192	13	12 192	15	5 516
10	1	5 005	4	5 005	7	2 478
11	1	5 503	6	5 503	6	2 737
	59	113 760	124	113 760	139	36 717
			$124 \pm 6\,06 \times 3$		$139 \pm 6\,06 \times 3$	

Table 23

Distribution of male and female individuals in the sibships, compared with the expected number, when *penile hypospadians* are interpreted in part as genetically male, in part as genetically female A better conformity is found, when the patients are interpreted as male

Sibship		Hypospadians				Number of sibships $\times \sigma^2$
		Interpreted as males		Interpreted as females		
Size of	Number of	Expected number of males	Actual number of males	Expected number of females	Actual number of females	
2	7	9 333	12	9 333	10	1 554
3	3	5 142	4	5 142	8	1 470
4	5	10 665	7	10 665	18	3 910
6	1	3 048	5	3 048	2	1 379
7	2	7 056	10	7 056	6	3 334
	18	35 244	38	35 244	44	11 647
			$38 \pm 3 \times 3\,41$		$44 \pm 3 \times 3\,41$	

Table 24

Distribution of male and female individuals in sibships, when *penoscrotal cases* are interpreted partly as male, partly as female individuals Good conformity with the expected number in the former, lacking conformity in the latter case.

Sibship		Hypospadians				Number of sibships $X\sigma^2$
		Interpreted as males		Interpreted as females		
Size of	Number of	Expected number of males	Actual number of males	Expected number of females	Actual number of females	
2	12	16 000	16	16 000	22	2 664
3	6	10 284	11	10 284	14	2 940
4	7	14 931	17	14 931	19	5 474
5	2	5 162	7	5 162	6	2 164
6	2	6 096	7	6 096	9	2 758
7	1	3 528	2	3 528	6	1 667
8	1	4 016	5	4 016	4	1 945
10	1	5 005	5	5 005	7	2 478
12	1	6 001	5	6 001	7	2 992
	33	71 023	75	71 023	94	25 082
			75 ± 3 × 5 00		94 ± 3 × 5 00	

Table 25

Distribution of male and female individuals in the sibships, when *perineo scrotal cases* are interpreted partly as male and partly as females individuals Good conformity with the expected number in the former, lacking conformity in the latter case

Sibship		Hypospadians				Number of sibships $X\sigma^2$
		Interpreted as males		Interpreted as females		
Size of	Number of	Expected number of males	Actual number of males	Expected number of females	Actual number of females	
2	6	8 000	10	8 000	8	1 332
3	3	5 142	5	5 142	8	1 470
4	2	4 266	3	4 266	7	1 564
5	1	2 581	2	2 581	1	1 082
6	1	3 048	3	3 048	4	1 379
11	1	5 503	3	5 503	9	2 478
		28 540	26	28 540	40	9 305
			26 ± 3 × 3 05		40 ± 3 × 3 05	

to the degree of the father's malformation This table shows also how many of the boys had been examined and how many were normal.

All degrees of hypospadias, apart from perineoscrotal cases, are represented There were normal boys in all groups, and the sex distribution did not differ from normal

Sex Distribution in Sibships Including Hypospadians

For each of the four varieties of hypospadias I calculated the expected number of male and female individuals among the patients' siblings, in part when the patients are interpreted as genetically male and in part when they are interpreted as genetically female This calculation was carried out by means of *Koller's* tables (*Koller* (1940)) The results are presented in Tables 22—25 with the actual number and the calculated standard deviation

In juxtaglandular, penoscrotal and perineoscrotal cases there is a statistically significant difference between the expected and actual number of females, when the hypospadians are interpreted as genetically female while good conformity is seen, when they are interpreted as genetically male In the penile cases, the numbers involved are too small to permit a statistical evaluation Even so, the results accord better when the hypospadians are considered genetically male

Occurrence of Sex-linked Recessive Characters in Hypospadians

Colour blindness is a common, recessive, sex-linked character in man Determined by the Ishihara test, it is said to occur in about 8 % of all males and in about 0 5 % of all females (*Waaler* (1927)) Therefore, a large number of the probands and their parents were examined for colour blindness by means of *Ishihara's* plates (1936) in an endeavour to determine the genetic sex of the hypospadians

The result is set out in Table 26 Colour blindness occurred in all

Table 26

Distribution of colour blindness among the hypospadians, their normal fathers and mothers

	Probands		Fathers		Mothers	
	Total	Colour blind	Total	Colour blind	Total	Colour blind
Juxtaglandular hypospadias	56	3	42	7	42	0
Penile hypospadias	*10*	*1*	*11*	*1*	*12*	*0*
Penoscrotal hypospadias	28	2	22	0	22	0
Perineoscrotal hypospadias	10	1	4	1	7	0
Total	*104*	7	*79*	*9*	*83*	*0*

degrees of hypospadias. When regard is paid to the small numbers involved there does not appear to be any difference in the incidence among the hypospadians and their fathers. Moreover the incidence — 6.73 (p_s in % is 18.03 and p_m in % 2.31) — does not differ from that applying to normal males. On the other hand it is too high for genetically female individuals.

If a colour blind hypospadian is interpreted as genetically female it must also be demanded — on account of the mode of inheritance of recessive sex linked characters — that the father is colour blind, provided that he cannot be interpreted as intersexual due to a genital malformation. In this series two colour blind patients with juxtaglandular and one with penile hypospadias had fathers with normal colour vision and normal genitals. One colour blind patient with perineoscrotal hypospadias had a father with a normal colour vision but with juxtaglandular hypospadias. In the last case both juxtaglandular and perineoscrotal cases of hypospadias would have to be interpreted as intersexes if the child with perineoscrotal hypospadias is to be interpreted as such. The fathers of the remaining colour blind hypospadians had died but as far as was known they had had normal colour vision and normal genitalia.

Therefore neither the sex distribution found among the children and the siblings of the hypospadians nor the incidence of the sex linked recessive character colour blindness indicate that hypospadias — mild or severe — should be on the whole interpretable as genetically intersexual.

Hormonal Intersexuality

It has been shown repeatedly in animal experiments that the normal development of the foetal genitals may be changed by the administration of sex hormones to the mother (cf. *Dantchakoff* (1938), *Greene* (1942, 1944), *Moore* (1944)). This even applies to species as superior as monkeys (*van Wagenen & Hamilton* (1943)). These experiments were carried out to elucidate the mechanism of the normal development of the genitals but they have also given rise to speculations regarding the aetiology and pathogenesis of genital malformations. Various authors have tried to relate the aetiology of the malformations to their theories regarding the normal sex differentiation. In addition to the gonads it has been suggested that the adrenals might be of significance in sex differentiation and development of intersexuality (*Broster* (1947)).

Despite marked divergences between the different views regarding the significance of hormones and their mode of action in the develop

Chapter 9

EXOGENOUS ÆTIOLOGICAL FACTORS

Recently, it has been realized that malformations may be the result of foetal infection with rubella (cf *Albaugh* (1945) *Bardram & Brændstrup* (1947)). Such malformations are mainly localized to the eyes, heart and brain but a few cases of hypospadias have been reported following maternal rubella during pregnancy (*Prendergast* (1946), *Keizer* (1950)). When considering the high incidence of hypospadias, however these may have been chance coincidences.

Also animal experiments have shown that exogenous factors may, via the maternal organism, cause malformation of a foetus. If pregnant experimental animals are exposed to vitamin deficiency, part of the litter will be born with malformations. The nature of such malformations depends on which vitamin is withdrawn from the diet (*Warkany* (1948)). Avitaminosis A has been followed by internal genital malformations (*Bendixen* (1944)). Even a quite brief oxygen deficiency may cause malformations. *Ingalls, Curley & Prindle* (1950) exposed pregnant mice to anoxia. Among their offspring congenital defects were far more common than in a control series. Malformations have also been induced by treating pregnant mice with cortisone. This resulted inter al. in harelip in the offspring (*Fraser & Fainstat* (1951)). The number of mice with harelip proved to depend upon which strain was used in the experiment. In other words, there must have been a certain interplay between genetic factors and the exogenous action of the cortisone. Toxic damage of the spermatozoon may also be mentioned among the causes of experimental malformations. Artificial insemination with spermatozoa treated with colchicine in low concentrations has resulted in offspring with a high incidence of spina bifida (*Nachtsheim* (1951)).

The nature of the malformation depends on the stage of foetal life at which the exogenous factor is active According to *Ingalls* experiments (1950) rapidly growing tissues sustained most damage In the case of rubella also the malformation depends on the time of the deleterious action (*Dods (1948)*) Moreover combined malformations may occur in tissues of the same embryological age (*Ipsen jr & Ohlels* (1932) *Grunfelder & Tasch* (1949))

As far as human malformations are concerned it is difficult to elucidate the nature of the exogenous factors It is impossible to procure a suitable material Birth records have the advantage that the history has been taken at the termination of pregnancy but the drawback that it has not been taken with a view to the aetiology of malformations This is obtained by taking the data from the parents of malformed children but in such cases many years may have passed from the pregnancy concerned so that presumably the data are not quite reliable

Writer s Investigations

Despite some scepticism regarding the possibility of demonstrating exogenous factors the writer perused the 90 records from Lying in Department B with such factors in mind Furthermore I interviewed the mothers of 34 hypospadians regarding the course of the pregnancy

If an exogenous factor is to be attributed with any significance it must have been active before the development of the urethra has been completed i e before the end of the fourth month of gestation (*Spaulding* (1921)) For this reason I looked only for abnormalities during the first four months of gestation

This material was perused with a view to

Infectious diseases which were not reported in any case

Avitaminoses of which I found no evidence Also there was no case of hyperemesis which might be imagined to cause vitamin deficiency

Somatic and psychic trauma No well defined cases

Hæmorrhages During the first four months there were 7 cases of hæmorrhage among 124 patients The hæmorrhage was however mild in all cases and the incidence is not high enough to be attributed with any significance

Intoxications The parents of a perineoscrotal hypospadian reported that they had both been under the influence of alcohol when the child was conceived

It will be seen that the present series permits no conclusions regarding the nature of the exogenous factors As mentioned above however the series was not particularly suitable for this purpose and despite

the negative findings, some of the factors mentioned may have been operative.

Seeing that infectious diseases are subject to seasonal variations, a seasonal variation in the incidence of hypospadias in the newborn might be expected if infection is an ætiological factor. Such a variation might also be imagined to be caused by a possible ætiological vitamin deficiency, as the supply of vitamins is at a minimum during the spring.

Therefore, the birth dates of the 262 hypospadians are presented in Table 29 compared with the expected number, calculated on the basis of the birth dates of boys born in 1944 (Statistique du Danemark, 1945). The difference between the actual and expected number is seen to be quite irregularly distributed on the 12 months of the year. The χ^2 test shows no significant difference between the actual and expected number of cases (F = 11, χ^2 = 11.08, 0.5 > p > 0.4).

Among the twin material there are 5 discordant cases in which the birth weight is known. In all these cases, the malformed twin had the lowest birth weight or 47.3, 51.2, 66.2, 92.5, and 94.6 % respectively of the healthy twin's weight.

Table 29

262 cases of hypospadias classified according to the month of birth compared with the expected number born in each month. No seasonal variation.

	Number of boys born in 1944	Cases of hypospadias Expected a	Actual x	$a - x$	$\frac{(a-x)^2}{a}$
January	3,896	21.32	30	− 8.68	3.5338
February	3,884	21.25	19	+ 2.25	0.2382
March	4,379	23.96	30	− 6.04	1.5226
April	4,195	22.95	19	+ 3.95	0.6798
May	4,142	22.67	17	+ 5.67	1.4181
June	3,915	21.42	25	− 3.58	0.5983
July	4,026	22.03	17	+ 5.03	1.1484
August	3,946	21.59	25	− 3.41	0.5385
September	3,924	21.47	23	− 1.53	0.1090
October	3,850	21.07	22	− 0.93	0.0410
November	3,790	20.74	17	+ 3.74	0.6744
December	3,934	21.53	18	+ 3.53	0.5787
	47,881	262.00	262		11.0808

Occasioned by this finding, the writer studied the birth weight of 90 hypospadians born in Lying-in Department B compared with that of all boys discharged alive every fifth year during the same period. These

values are set out in Table 30. True, this table shows a higher incidence than expected in the low and a lower incidence in the high weight groups, but the difference is not statistical ($f = 7$, $\chi^2 = 9.73$, $p = 0.3$).

Table 30

Birth weight of 90 hypospadians compared with that of 5593 normal boys discharged alive. No statistical difference

Birth weight	Control series number	Hypospadias: Expected number a	Hypospadias: Actual number x	$\frac{(a-x)^2}{a}$
Under 2500 g	512	8.2	11	0.8689
2550—2750 g	449	7.2	7	0.0066
2800—3000 g	704	11.3	14	0.6287
3050—3250 g	990	15.9	19	0.5916
3300—3500 g	1076	17.3	22	1.2670
3550—3750 g	870	14.0	9	1.7881
3800—4000 g	565	9.1	3	4.0800
over 4000 g	427	6.9	5	0.5076
	5593	90.0	90	9.738

Combination with Other Malformations

Other congenital defects occurred in 9 of the 173 probands, viz. three with juxtaglandular, two with penile, one with penoscrotal and three with perineoscrotal hypospadias.

On the basis of the small numbers involved it is impossible to state whether the incidence of other malformations is increased in hypospadians. If such a combination is to be explained on the basis of a common aetiological factor, the development of the affected organs must take place at the same foetal stage as that of the urethra, which is completed in the fourth month of gestation.

The other congenital defects were as follows:

Hardness of hearing due to a perceptive defect in three patients with juxtaglandular, penile and penoscrotal hypospadias respectively. The degree of hypospadias and deafness was proportional. As the inner ear has practically reached its definite form in the 8th foetal week (*Arey* (1942) p. 496) the juncture corresponds fairly well with that of the urethral development.

Harelip and cleft palate in two cases, one of juxtaglandular and one of perineoscrotal hypospadias. The union of the two halves of the palate usually takes place in the 9th foetal week (*Arey* (1942) p. 198).

This defect therefore may also be related chronologically to hypospadias

Megacolon and anal stricture in one case of familial juxtaglandular hypospadias Owing to the close relation between the development of the rectum and the urogenital organs it is natural to relate these two malformations to each other

Clubfoot in the last mentioned patient and in one with perineoscrotal hypospadias *In the latter case clubfoot as well as hypospadias were* familial It is impossible to state whether clubfoot and hypospadias *may be related ætiologically True the development of the limbs sets* in at a very early stage but that of the skeleton of the foot ranges over a very long period

Feeblemindedness in two cases A patient with penile hypospadias suffered from mild feeblemindedness which occurred also among other members of the otherwise intelligent family The other patient with perineoscrotal hypospadias was an imbecile This patient also had Little s disease Therefore it cannot be ruled out that the feeble mindedness may have been due to birth injury

A number of the congenital defects encountered in the hypospadians may be explained as developmental arrest due to one or more inhibitory factors which at the same time have arrested the development of the genitals The ætiological factors may also be imagined to have given rise to a generalized inhibition of growth At least this would explain why the hypospadian among a pair of discordant twins is invariably the smaller one These presumptions however do not receive sufficient support from the present material

Chapter 10

CONCLUSION AND DISCUSSION OF THE PRACTICAL SIGNIFICANCE OF THE RESULTS

Although the aetiology of hypospadias has not been fully elucidated the results of the present study are of practical significance from the point of view of eugenics as well as operative criteria.

Before discussing these aspects the author would like to give a brief summary of the results.

Conclusion

Hypospadias is a congenital defect occurring in about 0.33 % of the male population. There are mild and severe cases with even transitions. The foreskin and urethra are invariably deformed, but the other external as well as the internal genitals may also be involved. For example, retention of the testes is a common associated phenomenon. Hypospadians marry as often as do normal men. In mild cases their sexual relations are normal, whereas in severe cases surgical correction of the penile flexion is required. The fertility is normal in mild cases, decreasing with increasing severity of the defect. The lesion is familial in about one-quarter of all cases, and within the same family there may be wide variations in degree. As far as the aetiology is concerned, both endogenous — inherited — and unknown exogenous factors must be considered. The mode of inheritance appears to be recessive with failing manifestation. The patients' genetic sex is male. They cannot be interpreted as intersexes according to Goldschmidt's theory.

Eugenic Measures

In Denmark it is permitted to interrupt a pregnancy when there is a risk that the child will be affected with a serious incurable inherited

disease The criteria must, thus be based on the risk as well as on the more or less serious nature of the disease.

Since the heredity of hypospadias appears to be recessive with failing manifestation, the risk of familial cases is slight It is highest for the brothers of a hypospadian, but at the mode of inheritance mentioned, it does not by any means reach 25 % In other words, if a couple have had one child with hypospadias, the risk that their next child will be affected has been reduced to considerably less than 12 5 %, as the ratio *boys/girls in these* sibships does not differ from normal The next highest risk will be found in the group sons of hypospadians In this group, however, the risk is far lower than among the brothers

But regard must be paid also to the nature of the lesion The fact is that only about 25 % of the patients have complaints necessitating surgical correction The latter has caused some difficulty in the course of time, but recently good results have been obtained, also in Denmark (*Fogh-Andersen* (1953)).

Hypospadias, therefore, is probably not an indication for interruption not even in the most severe cases Owing to the intrafamilial variation, *it is impossible to tell how severe the next case in the family* will be

In the general run of eugenic consultation, there is probably no reason to advise against having children or against marriage between first cousins, even though the male partner is affected with hypospadias

Since about three-quarters of the patients have shown normal fertility and since there is intrafamilial variation in the severity, the absence of eugenic measures will probably not have much influence on the incidence of the defect or on the distribution of mild and severe cases

Operative Indications

According to these eugenic considerations, there is hardly any reason to deprive hypospadians of the pleasure of having children Therefore, the possibility of improving a reduced fertility must be taken into consideration in setting up the *operative indications*

Juxtaglandular cases require no treatment apart from dilatation and perhaps meatotomy of a constricted orifice The difficulty of micturition is slight and fertility as well as sexual function normal Penile hypospadias is a transitional variety, in each individual case the advisability of surgical treatment must be considered. In more severe cases, the flexion of the penis has to be straightened to render sexual functions

normal, and reconstruction of the urethra is required to obviate difficulties of micturition and improve the fertility

In other words, three-quarters of all cases require no treatment The new surgical procedures for juxtaglandular hypospadias which are still being worked out (*Nahoum* (1947), *Brendler* (1948)) must be taken as contributions to cosmetic surgery The treatment of the last one-quarter demands experience and care It is therefore worth considering whether the approximately 30 new cases annually should not be centralized in a few departments

SUMMARY

Introduction

The main object of the present study was to elucidate the ætiology of hypospadias

Chapter 1

Reviewing the morphological features of the disease the writer finds an even transition between the mild and severe degrees For the purposes of the present work it is most practical to subdivide the condition into juxtaglandular penile penoscrotal and perineoscrotal cases The incidence of complicating retention of the testes among 274 hypospadians is compared with the incidence among the general Danish population This reveals an increased incidence of retention in all degrees of hypospadias

Chapter 2

After reviewing previous studies on the incidence of hypospadias the writer reports his own findings Ninety cases occurred among 27 613 baby boys aged about 10 days This is taken to represent the incidence among the total male population as there is no reason to believe that the mortality among hypospadians is particularly high About three quarters of the cases were *juxtaglandular about one eighth penile and* about one eighth penoscrotal or perineoscrotal

Chapter 3

The views regarding the fertility of hypospadians advanced so far have been based mainly on theoretical considerations In the present study the frequency of marriage among 77 patients over 20 years of age proved to accord with that among the general male population The patients *sexual relations do not* appear to differ essentially from normal once surgical correction of the severe forms of penile flexion has

been accomplished. The fertility of 47 married patients in relation to the severity of their defect proved normal in juxtaglandular — and perhaps also in penile — cases, whereas in more severe cases it was reduced but not abolished.

Chapter 4

Previous genetic studies consist of case reports comprising more or less thoroughly investigated families and twin series — apart from Lamy's series of 10 pairs of twins. Therefore, although indicated by various findings, the hereditary nature of the lesion has not been proved so far. Exogenous factors must be presumed to play a part, as Lamy reported discordance in three out of six pairs of monozygotic twins.

Chapter 5

To study the genetic aspect the writer collected a proband and a twin series. Out of 173 proband families 103 were examined, 43 partially examined, while 27 had to be ruled out. The genitals of the male relatives were examined except in 4.8 % who refused to submit to the examination.

Chapter 6

The familial cases are presented in pedigrees and the solitary ones in tables. The number of males examined and not examined in each family is given. The study of the 12 pairs of twins is reported.

Chapter 7

The material is considered as a whole, since there is familial occurrence in all degrees of the lesion — in an average of about 28 % — and marked intrafamilial variation in the severity. The defect is interpreted as an inherited lesion, as the incidence was increased among the probands' relatives and as concordance was found more often in monozygotic than dizygotic twins.

The writer compares the degree of manifestation in the twin series with the degree of manifestation calculated on the basis of the actual findings and the number of cases expected among the close relatives at dominant and recessive heredity respectively. This calculation indicated recessive heredity with failing manifestation.

It cannot be ruled out that some instances are of purely exogenous origin.

Consanguinity occurred in three out of 124 patients' parents (2.4 %).

Chapter 8

This chapter deals with Goldschmidt's intersexuality theory and certain views regarding the relation of hypospadias to this theory If hypospadians are intersexes according to this theory, their genetic sex must be female The writer, therefore, set out to study the sex distribution among the children and siblings of the hypospadians in the present series According to the findings, hypospadians cannot be interpreted as female individuals The distribution of a sex-linked recessive character — in this case colour blindness — among the patients and their parents also does not accord with the view that hypospadias is a form of intersexuality according to the theory of Goldschmidt

The mothers data regarding hormonal disturbances during pregnancy were studied This gave no evidence to interpret hypospadias as a hormonal form of intersexuality The age distribution among the mothers does not differ from that expected

Chapter 9

Perusal of 90 birth records and data regarding the pregnancy of 34 mothers afforded no reason to attach ætiological significance to foetal infections defective nutrition somatic or psychic traumas, intoxications or hæmorrhages during pregnancy

Reporting the complicating malformations in the present series, the writer tries to relate them to the hypospadias

In the five cases of discordant twins whose birth weight is known, the malformed twin was the smaller one On the other hand the birth weight of hypospadians on the whole did not differ from the expected values

Chapter 10

Eugenics and operative indications are discussed There is no indication for eugenic measures There is no reason to advise hypospadians against having children The possibility of improving the fertility, if reduced must therefore be included in one's contemplations regarding the operative indications In the author's opinion, there is no indication to operate in juxtaglandular cases

RESUME

Indledning

Arbejdets formål er hovedsageligt at belyse hypospadiens ætiologi

Kapitel 1

Ved en gennemgang af lidelsens morfologi påpeges, at der findes en jævn overgang mellem lette og svære grader For det foreliggende arbejde er det mest praktiske en inddeling i juxtaglandære, penile, penoscrotale og perineale tilfælde Differentialdiagnosen diskuteres på basis af egne tilfælde Hyppigheden af komplicerende testisretention hos 274 hypospadipatienter sammenlignes med testisretentionens hyppighed i den danske befolkning Herved findes forøget hyppighed af testisretention for alle hypospadigrader

Kapitel 2

Efter en kritisk gennemgang af tidligere undersøgelser over hypospadiens hyppighed, gøres rede for egne undersøgelser Ved disse fandt man 90 tilfælde blandt 27 613 ca 10 dage gamle drengebørn Denne hyppighed benyttes som et udtryk for hyppigheden i den samlede mandlige befolkning da hypospadipatienter næppe har nogen overdødelighed Man finder, at ca 3/4 af tilfældene er juxtaglandære, ca 1/8 penile og ca 1/8 penoscrotale og perineoscrotale

Kapitel 3

De tidligere anskuelser om hypospadipatienters fertilitet, der væsentligt er baseret på teoretiske betragtninger, omtales I egne undersøgelser findes hyppigheden af ægteskaber for 77 patienter over 20 år at stemme overens med hyppigheden af ægteskaber i den mandlige befolkning Patienternes seksuelle forhold synes ikke at afvige væsentligt fra det normale, når en sværere krumning af penis er operativt udrettet

Og ved en vurdering af 47 gifte patienters fertilitet sammenholdt med deres misdannelses sværhed findes normal fertilitet for de juxtaglandære — og måske de penile — tilfælde, for de sværere nedsat, men ikke ophævet fertilitet

Kapitel 4

Da de tidligere undersøgelser over arveligheden består af kasuistiske meddelelser om mere eller mindre *velundersøgte slægter og tvillingpar*, bortset fra Lamy's tvillingmateriale på 10 par, er det ikke tidligere bevist, at hypospadi er arvelig, selvom forskellige forhold taler herfor Exogene faktorer er formentlig af betydning, da Lamy fandt diskordans *i 3 af de 6 cenæggede tvillingpar*

Kapitel 5

Til arbejdets arvelighedsundersøgelse er indsamlet et proband- og et tvillingmateriale Af 173 probandslægter er 103 undersøgte, 43 delvist undersøgte, medens 27 udgår De mandlinge slægtninges genitalia er undersøgte, dog har 4,8 % af de opsøgte slægtninge afslået en sådan *undersøgelse*

Kapitel 6

De familiære tilfælde er illustreret ved slægtsskemaer og de solitære er opstillet i tabeller Antallet af undersøgte og ikke undersøgte mandlige slægtninge er markeret i hver enkelt slægt Undersøgelsen af de 12 tvillingpar er anført

Kapitel 7

Materialet vurderes under et, da der findes familiær forekomst for alle grader af lidelsen — gennemsnitlig i ca 28 % — og der forekommer en betydelig intrafamiliær variation i tilfældenes sværhed Man anser lidelsen for arvelig, da den findes med forøget hyppighed blandt probandernes slægtninge, og eenæggede tvillingpar hyppigere end toæggede udviser konkordans

Manifestationsgraden i tvillingmaterialet og manifestationsgraden, udregnet på basis af det fundne og det for henholdsvis dominant og recessiv arvegang forventede antal tilfælde i de nærmeste slægtningegrupper sammenlignes Herved findes størst sandsynlighed for recessiv arvegang med svigtende manifestation

Det kan ikke udelukkes at nogle tilfælde er rent exogent betingede

Indgifte fandtes hos 3 af 124 patienters forældre (2,4 %)

Kapitel 8

Goldschmidts intersexualitetsteori og nogle anskuelser om hypospadiens relation til denne omtales. Er hypospadipatienter intersexer efter denne teori, må deres genetiske køn være hunligt. I dette materiale har man derfor undersøgt kønsfordelingen blandt hypospadipatienternes børn og i deres søskendeflokke. Disse fordelinger tillader ikke at hypospadipatienter opfattes som hunlige individer. Fordelingen af en kønsbundet recessiv egenskab som farveblindhed blandt patienterne og deres forældre stemmer heller ikke overens med anskuelsen om hypospadi som en intersexualitetsform efter Goldschmidts teori.

Man har gennemgået oplysninger om mødrene med henblik på hormonale forstyrrelser. Der blev i dette materiale ikke fundet holdepunkter for at hypospadi kunne opfattes som en hormonal intersexualitetsform. Fordelingen af mødrenes alder afviger ikke fra den forventede.

Kapitel 9

Ved en gennemgang af 90 fødejournaler og oplysninger om 34 mødres graviditet findes ingen holdepunkter for at føtale infektioner, ernæringsmangler, somatiske eller psykiske traumer, intoxicationer eller blødninger i svangerskabet er af ætiologisk betydning.

De komplicerende misdannelser i eget materiale omtales, og man søger at sætte udviklingen af disse i relation til udviklingen af hypospadi.

Fødselsvægten var mindst hos den misdannede tvilling i de 5 af materialets tvillingpar med diskordans, hvor man havde oplysninger om fødselsvægten. Men 90 hypospadipatienters fødselsvægt afveg ikke fra det forventede.

Kapitel 10

Arvehygiejne og operationsindikationer diskuteres. Der er ikke indikation for arvehygiejniske forholdsregler. Der er ingen grund til at fraråde hypospadipatienter at få børn. Muligheden af at bedre en evt. nedsat fertilitet må derfor inddrages i overvejelserne om operationsindikation. Man finder det ikke indiceret at operere de juxtaglandære tilfælde.

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